

New Onset Hallucinations with Mirtazapine: A Case Report

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Abstract Introduction: Mirtazapine is an antidepressant commonly used and considered safe in the elderly. It is favored in elderly patients suffering from insomnia and weight loss secondary to depression. Here, we present a case where mirtazapine caused an unexpected adverse effect of agitation and hallucinations contrary to the expected reaction of sedation. Case Presentation: An 86 year old female was admitted with complaints of poor oral intake. She was very frail and weighed 23 kilos. She was malnourished and suffering from hypoalbuminemia and electrolyte abnormalities. Her evaluation did not reveal an organic cause for weight loss. Her cognition was intact. She was started on mirtazapine 7.5 mg for depression and received 2 doses. During the second night, she was unable to sleep and started having visual hallucinations. The hallucinations were described as people in the wall, boxes, and cars coming from the window to hit her. Subsequently Mirtazapine was discontinued and hallucinations stopped 48 hours after the last dose. Discussion: Mirtazapine is a tetracyclic antidepressant with serotonergic and noradrenergic activity. Mirtazapine has been shown to be very effective in treating depression in elderly. The decision to treat with mirtazapine is also based on its side effect profile. Somnolence happens in 50 % of people and weight gain in 15% of patients. Therefore mirtazapine is commonly used to treat depression in patients with concomitant insomnia and anorexia. The relative tolerability of mirtazapine makes it a first-line medication for many elderly with major depression. Peak plasma concentrations are reached within 2.2 to 3.1 hours after single oral doses of 15 to 75mg. Mirtazapine is extensively metabolized in the liver. Protein binding is 85%. Mean elimination half-life is 22 hours, so it can be administered once a day. Despite its known sedative effect, there have been reports of visual and auditory hallucinations and insomnia occurring with the use of mirtazapine, which could be related to increase in dopamine levels in the frontal cortex. Our patient was elderly, frail and malnourished. Her hypoalbuminemia related to malnutrition and low protein binding could also be a factor as increased free drug will be available to enter the CNS. Although she was started at half the adult dose, it may still have been high for her due to her low weight. Per the Naranjo criteria, Mirtazapine was determined as the probable cause of hallucination in this case. This case illustrates that although Mirtazapine is a relatively safe drug to use in elderly, we need to be cautious when starting the drug or increasing the dose, especially in malnourished patients.

Keywords: Mirtazapine, elderly, adverse effect, hallucinations, malnourished

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1. Introduction

Depression in the elderly is a common and serious health problem and is associated with significant comorbidity, poor functioning and excessive use of healthcare resources [1]. It is also frequently underdiagnosed and undertreated [2]. Efficacious therapy is available for late life depression. Mirtazapine is a commonly used drug in the elderly and also a preferred one, based on relatively good tolerability, and side-effect profile of sedation and weight gain [3]. Here, we present a case where mirtazapine caused an unexpected adverse effect of agitation and hallucinations contrary to the expected reaction of sedation.

2. Case Report

An 81 year old female was admitted with complaints of poor oral intake for the past week, and fatigue. She had been admitted 2 months prior also with poor intake and dehydration. Her past medical history was unremarkable except for osteoarthritis, and anemia on iron and vitamin B12 supplementation. Examination showed a very pale, cachectic lady weighing only 23 kilos. Her vital signs were all within the normal range and physical examination was unremarkable except for cachexia and osteoarthritic changes in bilateral knees. Her cognition was intact. Rapid screen for depression with PHQ-2 questionnaire was positive. Investigations showed chronic anemia, hypoalbuminemia,

and hypernatremia secondary to dehydration. Her evaluation did not reveal an organic cause for weight loss.

Based on her relatively benign examination and investigation results, her clinical condition of anorexia and malnutrition was considered to be secondary to depression. Due to her chronic anorexia, mirtazapine was chosen as the preferred antidepressant for her. She was started on mirtazapine 7.5 mg for depression and received 2 doses. After the second dose, a dramatic change was noticed by the family and healthcare workers. She was completely unable to sleep and started having visual hallucinations and agitation. The hallucinations were described as people in the wall, boxes, and cars coming from the window to hit her. Subsequently Mirtazapine was discontinued and hallucinations stopped 48 hours after the last dose.

3. Discussion

Mirtazapine is an atypical antidepressant. It is a tetracyclic antidepressant with serotonergic and noradrenergic activity. It increases noradrenergic and serotonergic neurotransmission via blockade of central α_2 receptors. The increased release of serotonin (5 hydroxytryptamine; 5-HT) stimulates serotonin 5-HT₁ receptors because mirtazapine directly blocks 5-HT₂ and 5-HT₃ receptors. The increased noradrenergic and 5-HT₁ receptor-mediated neurotransmission is thought to be responsible for the antidepressant activity of mirtazapine. This mechanism of action maintains equivalent antidepressant efficacy but minimizes many of the adverse effects common to both tricyclic antidepressants and selective serotonin reuptake inhibitors [4].

Mirtazapine has been shown to be very effective in treating depression in elderly. In a meta-analysis of 29 randomized controlled trials, Mirtazapine was reported to have a faster onset of action and showed improved results in the acute treatment of depression compared to selective-serotonin reuptake inhibitors (SSRI) and venlafaxine, another serotonin-norepinephrine reuptake inhibitor (SNRI) [5]. The decision to treat with mirtazapine is also based on its side effect profile. Somnolence happens in 50 % and weight gain in 15% of patients treated with mirtazapine [3]. Mirtazapine was significantly more likely to cause weight gain or increased appetite (Relative Risk [RR]:3.68) and somnolence (RR: 1.62) compared to SSRIs, and less likely to cause sleep disturbance (RR: 0.03) compared to the Venlafaxine [6]. Therefore mirtazapine is commonly used to treat depression in patients with concomitant insomnia and anorexia [7]. The relative tolerability of mirtazapine makes it a first-line medication for many elderly with major depression.

Plasma protein binding of Mirtazapine is 85%. Gender and age affect metabolism with females and elderly showing a higher plasma concentration [8]. Peak plasma concentrations of Mirtazapine are reached within 2.2 to 3.1 hours after single oral doses of 15 to 75mg. It is extensively metabolized in the liver. Mean elimination half-life is 22 hours, so it can be administered once a day. The recommended starting dosage of mirtazapine is 15 mg/day for 4 days, then 30 mg/day for 10 days [3].

Despite its known sedative effect, there have been reports of delirium and visual and auditory hallucinations

and insomnia occurring with the use of mirtazapine. Although different mechanisms have been proposed to explain this effect of mirtazapine, one plausible reason seems to be related to increase in dopamine levels in the frontal cortex [7]. This is due to α_2 adrenergic blockade causing increased release of norepinephrine and dopamine. Dopamine is thought to play a role in psychosis and antipsychotics mainly work by blockade of dopamine receptors [9].

Our patient was an elderly female, frail and malnourished. Her albumin level was low at 20 g/L, and total protein level was 43 g/L. Low plasma protein levels would lead to higher free drug plasma concentrations and therefore increased free drug would be available to enter the central nervous system. Although she was started at half the recommended adult starting dose, it may still have been high for her due to her low weight. Due to the rapid onset of action and elimination, effects were noticed as soon as after the second dose and also resolved within 48 hours. The Naranjo criteria [10] were used to determine that Mirtazapine was the probable cause of hallucination in this case. This case illustrates that although Mirtazapine is a relatively safe drug to use in elderly, we need to be very cautious when starting the drug or increasing the dose, especially in severely malnourished patients.

4. Conclusion

In this case report, we present an elderly, frail and malnourished patient who developed hallucinations shortly after initiation of the atypical antidepressant, Mirtazapine. Mirtazapine is a relatively safe drug, however, there needs to be caution regarding adverse effects, especially in elderly, malnourished patients.

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