Print ISSN: 2319-2003 | Online ISSN: 2279-0780

IJBCP International Journal of Basic & Clinical Pharmacology

DOI: http://dx.doi.org/10.18203/2319-2003.ijbcp20163274

Case Report

Paradoxical nocturnal agitation associated with mirtazapine therapy

Olayinka A. Ogundipe, Zubaidat M. Oduniyi*

Department of Medicine of the Elderly, Royal Infirmary of Edinburgh, 51 Little France Crescent, Edinburgh, Scotland EH16 4SA

Received: 30 July 2016
Accepted: 31 August 2016

***Correspondence to:**
Dr. Zubaidat M. Oduniyi,
Email: zmoduniyi@hotmail.co.uk

ABSTRACT

This report describes an 85 year old woman presenting with a mixed delirium with risk factors of hyponatraemia, polypharmacy, and bilateral frontal lobe atrophy with small vessel cerebrovascular disease. Treatment for depression with oral citalopram had been revised to oral mirtazapine, with the aim of reducing the risks of recurrent hyponatraemia noted with the former. She developed an evolving adverse drug reaction (ADR) symptom profile of insomnia, and later severe paradoxical nocturnal agitation. These symptoms were subsequently noted to correlate with both the night-time dosing pattern, and the increased dosing regimen of the mirtazapine. The symptoms settled rapidly following withdrawal of the mirtazapine. The report briefly reviews the relevant literature, and two previously validated causality assessment systems are applied to the index case to support the pharmacovigilance process. This is aimed at promoting objectivity in assessing for the likelihood that the suspected medication (mirtazapine) was the cause for the noted adverse drug reaction.

Keywords: ADR, Agitation, Anti-depressant, Causality assessment system, Delirium, Depression, Insomnia, Mirtazapine, Pharmacovigilance

INTRODUCTION

Mirtazapine is a pharmacological agent used, in a range of doses, as a treatment option for depression in adult and older age range patients. This report describes an older patient in whom paradoxical nocturnal agitations were associated with the use of mirtazapine.

CASE REPORT

An 85-year old Caucasian woman was admitted to hospital for assessment of an acute alteration to her mental status, inattention, and accompanying fluctuant hypo - / hyperactivity of one day's duration. Her medical history was notable for depression; iron deficiency anaemia (nutritional); gout, previous right nephrectomy for a non-functioning kidney due to chronic obstructive hydronephrosis; and left ureteric stenting for stricture-associated left hydronephrosis. Other relevant history included hypothyroidism, atrial fibrillation (AF) and rheumatic fever in childhood with resultant valvular heart disease (echocardiography signs of severe aortic stenosis, mixed mitral valve disease and left ventricular systolic dysfunction).

Medication on admission were

citalopram 10 mg daily, furosemide 20 mg daily, paracetamol 500 mg four times daily, levothyroxine 50 micrograms daily, warfarin average 1.5 mg daily for AF, pravastatin 40 mg daily, colchicine 500 micrograms daily (low dose maintenance therapy for gout), perindopril 2 mg daily, cetirizine 10 mg daily.

Her weight was 50.8 kg, height 1.62 metres, and a derived body mass index (BMI) of 19.4.

Blood tests on admission showed

Urea 5.4 mmol/L (2.5 - 6.6); creatinine 102 umol/L (60 - 120); sodium 128 mmol/L (135 - 145); potassium 5.2 mmol/L (3.6 - 5.0); estimated glomerular filtration rate (eGFR) 45 ml/min (> 60 ml/min/1.73 m^2).

Other tests revealed that full blood count and serum B12 were normal. Iron studies showed ferritin 40 ug/L (20 - 300); serum iron 6 umol/L (10 - 32); Transferrin 2.58 g/L (2.0 - 4.0) and Transferrin saturations 9%. Serum folate was 2.5 ug/L (2.8 - 20); serum magnesium 0.72 mmol/L (0.7 - 1.0); and serum urate level 0.46 mmol/L (0.12 - 0.36). Thyroid function tests indicated optimal supplementation. Serum albumin, calcium and phosphate were normal. Serum bilirubin and alanine aminotransferase (ALT) were also normal. The International normalised ratio (INR) was 2.1 (on warfarin).

Urine cultures showed no significant growth.

Resting 12 lead electrocardiogram (ECG) showed AF, ventricular rate of ~ 60 bpm; but an otherwise unremarkable trace.

Plain chest radiograph indicated cardiomegaly. computerised tomography (CT) brain scan showed evidence of small vessel cerebrovascular disease with cerebral cortical atrophy that was predominant in the frontal lobes.

Collateral history from her next of kin did not suggest alcohol excess or nicotine withdrawal.

A clinical diagnosis of mixed pattern delirium was entertained, with notable risk factors being hyponatraemia, polypharmacy, bilateral frontal lobe atrophy with small vessel cerebrovascular disease.

Furosemide and citalopram were withheld on account of the hyponatraemia and associated delirium. Cetirizine was also temporarily withheld on account of possible contributory anticholinergic side-effects relevant to the on-going delirium. Oral supplementation with folic acid 5 mg daily and ferrous fumarate 210 mg thrice daily were introduced, and nutritional reviews were undertaken.

The hyponatraemia and hyperkalemia resolved fully and uneventfully over the subsequent 48 hours of withdrawal of the above medications; as did the hyponatraemia-associated delirium.

Based on on-going depression with significant somatic symptoms, oral mirtazapine (generic formulation) was introduced at the dose of 15 mg at night. Mirtazapine was substituted for citalopram, aiming to reduce the risks of precipitating recurrent hyponatraemia. After four initial doses of 15 mg at night, the mirtazapine was rapidly up-titrated to the target maintenance dose of 30 mg at night.

A behaviour chart had been maintained as part of the assessment of the delirium and depression, and this proved particularly helpful in providing added objectivity to the determination of the cause and temporal timelines of her evolving condition. The behaviour chart was collated by multiple observers, making individual entries, spread across 24 hours, and cumulatively derived over a 21- day period.

After the mirtazapine was introduced, she was noted to have some insomnia, but this did not raise much attention as it was felt this might be due to the change in environment from home to hospital, which might have disturbed her usual sleep pattern/rhythm. However, when the mirtazapine dose was subsequently increased, she was noted to develop new onset symptoms of severe agitation with a clear nocturnal pattern. The symptoms were intermittent and the pattern closely mirrored the predictable nightly and hospital nurse supervised administration of oral mirtazapine.

In relation to timelines, the symptoms of severe nocturnal agitation were notably marked after eight days of introducing oral mirtazapine (timed from the lower 15 mg dose), and that corresponded to four days after she had been receiving the 30 mg dose. As earlier stated, the period of her receiving the lower 15 mg nightly dose had been relatively unremarkable.

Ultimately, a clinical decision was taken to withdraw the mirtazapine in view of the strong correlation with the severe nocturnal paradoxical agitation. This corresponded to a total of 11 days after its initial introduction (timed from the lower nightly dose of 15 mg), and a total of seven days after the increment to the 30 mg nightly dose.

The mirtazapine associated adverse drug reactions (ADRs)/symptoms of severe nocturnal agitation and insomnia resolved within 24 hours of discontinuation of the medication. She opted for a trial without anti-depressants and to re-evaluate her symptom profile with non-pharmacological options, including access to community-based old age psychiatry services.

She completed a period of comprehensive geriatric assessment. She remained fairly settled over the subsequent two-week periods and with no further acute clinical concerns up till her discharge from the acute hospital after a period of rehabilitation.

DISCUSSION

Mirtazapine is a pharmacological agent that has occasionally been sub-classified as an ‘other’ or ‘atypical’ antidepressant. It has also been described as possessing central noradrenergic and serotonergic properties.[1,2] It has

been described as having a low anti-cholinergic side-effect profile, and this property potentially makes it more attractive in the management of selected cases of depression in older patients; especially where it is often important to consider the added risks of precipitating delirium.[1]

Some basic pharmacodynamic and pharmacokinetic considerations

Mirtazapine is available in oral formulation, and has good bioavailability via the gastrointestinal route. It has a long half-life (20 - 40 hours); undergoes significant hepatic metabolism; is excreted via the urine (the predominant route at ~ 75%) but also via faeces (to a lesser extent).[2] Both the metabolism and elimination of mirtazapine could thus be potentially influenced by hepatic and/or renal impairment.[1,2]

Mirtazapine has earned a place in the pharmacological armoury of managing major depression and has a reasonable profile, both in terms of rapidity of onset of action and the attainment of therapeutic benefits. It also has a reasonable overall side-effect profile.[1,2]

Some of the more commonly reported side-effects of mirtazapine include increased appetite, weight gain, dry mouth, dizziness, postural hypotension, drowsiness and/or somnolence (especially on initiation), insomnia, abnormal dreams and confusion.[1]

The index case report serves as clinical reminder of another rare neuropsychiatric side-effect (paradoxical nocturnal agitation). As illustrated by this case, this side-effect (if recognised) could have a significant (but reversible) impact upon a patient's quality of life.

Application of ADR causality assessment systems

The use of previously validated causality assessment systems in the review of ADR-related case reports could promote enhanced objectivity when medications are suspected of, or reported as being associated with ADRs.[3-5] These systems are not perfect, but could nevertheless support and potentially enhance pharmacovigilance related assessment and reporting. The application of the Naranjo adverse drug reaction probability scale (Table 1) to the index case report, translates into a score of 5, which equates to a 'probable' ADR classification.[3,4]

The stringent application of another validated causality assessment system, i.e. the WHO-UMC method, translates to a 'possible' ADR classification for the index case report (see Table 2).[6,7]

Table 1: Naranjo ADRS algorithm.

Questionnaire applied to index case report
Are there previous conclusive reports on this reaction? Yes (+1) No (0) Do not know or not done (0)
Did the adverse event appear after the suspected drug was given? Yes (+2) No (-1) Do not know or not done (0)
Did the adverse reaction improve when the drug was discontinued or a specific antagonist was given? Yes (+1) No (0) Do not know or not done (0)
Did the adverse reaction appear when the drug was re-administered? Yes (+2) No (-2) Do not know or not done (0)
Are there alternative causes that could have caused the reaction? Yes (-1) No (+2) Do not know or not done (0)
Did the reaction reappear when a placebo was given? Yes (-1) No (+1) Do not know or not done (0)
Was the drug detected in any body fluid in toxic concentrations? Yes (+1) No (0) Do not know or not done (0)
Was the reaction more severe when the dose was increased or less severe when the dose was decreased? Yes (+1) No (0) Do not know or not done (0)
Did the patient have a similar reaction to the same or similar drugs in any previous exposure? Yes (+1) No (0) Do not know or not done (0)
Was the adverse event confirmed by any objective evidence? Yes (+1) No (0) Do not know or not done (0)
Derived total score of 3 translates to a classification of a possible adverse drug reaction (ADR)
> 9 = definite ADR
5 - 8 = probable ADR
1 - 4 = possible ADR
0 = doubtful ADR

Table 2: WHO-UMC causality categories.

Causality term	Causality term assessment criteria*
Certain	• Event or laboratory test abnormality, with plausible time relationship to drug intake • Cannot be explained by disease or other drugs • Response to withdrawal plausible (pharmacologically, pathologically) • Event definitive pharmacologically or phenomenologically (i.e. an objective and specific medical disorder or a recognised pharmacological phenomenon) • Rechallenge satisfactory, if necessary
Probable/likely	• Event or laboratory test abnormality, with reasonable time relationship to drug intake • Unlikely to be attributed to disease or other drugs • Response to withdrawal clinically reasonable • Re-challenge not required
Possible	• Event or laboratory test abnormality, with reasonable time relationship to drug intake • Could also be explained by disease or other drugs • Information on drug withdrawal may be lacking or unclear
Unlikely	• Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible) • Disease or other drugs provide plausible explanations
Conditional/ unclassified	• Event or laboratory test abnormality • More data for proper assessment needed, or • Additional data under examination
Unassessable/ unclassifiable	• Report suggesting an adverse reaction • Cannot be judged because information is insufficient or contradictory • Data cannot be supplemented or verified

(WHO. The Upsalla Monitoring Centre - UMC); * All points should be reasonably complied with.

Key Points

- Neuropsychiatric ADRs such as severe paradoxical agitation and insomnia are rare but clinically important potential side-effects associated with mirtazapine therapy.
- The presentation of such ADRs may be insidious, variable in frequency and severity; and this in turn calls for a higher index of suspicion as it could be potentially easier to overlook.
- As in this case, the clinical history should be periodically reviewed, as an association might be noted between the dosing regimen adopted and the pattern of ADRs noted or described by patients (or carer-providers).
- The neuropsychiatric ADRs noted in this index case report were noted to be fully and rapidly reversible upon cessation of the use of mirtazapine.
- The use of validated causality assessment systems could serve as an important component towards improving objectivity in pharmacovigilance related case reporting; and/or when ADRs are described in association with medication use.

CONCLUSION

This report focuses on a patient with mirtazapine-associated neuropsychiatric ADRs of severe nocturnal agitation. The case is intended as a clinical reminder; with practical relevance to a wide range of clinicians e.g. those who care for older patients in either community or hospital settings. We would suggest that targeted and early review of patients' symptom profiles is considered by prescribers of mirtazapine for depression. This is particularly relevant if its use is considered in patients who are judged to have significant risks factors for delirium, or in those who present with delirium.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

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Cite this article as: Ogundipe OA, Oduniyi ZM. Paradoxical nocturnal agitation associated with mirtazapine therapy. Int J Basic Clin Pharmacol 2016;5:2271-5.