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Progress in Neurology and Psychiatry

CASE NOTES

Olanzapine-Induced Pedal Oedema With Delayed Resolution: A Case Report and Review of Literature

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ABSTRACT

Olanzapine can have a better impact on negative symptoms of schizophrenia with reduced motor side effects compared to other atypical antipsychotics, according to some literature. Here, the authors describe a case of a woman with a diagnosis of schizophrenia who developed the rare side effect of bilateral pedal oedema while on oral olanzapine. The possible mechanism behind the condition and the clinical management measures taken to resolve the oedema is discussed.

Olanzapine is an atypical antipsychotic often used in the mental health management of psychotic disorders. It is suggested in some literature to have a better effect on negative symptoms of schizophrenia compared to other atypical antipsychotics [1, 2]. Its action on Dopamine 2 receptors helps reduce the positive symptoms of psychosis. In contrast, its action on Serotonin 2A receptors enhances dopamine release in specific brain regions, reducing the motor side effects common with typical antipsychotics. It also acts on muscarinic, histaminergic, and α-adrenergic receptors, which are responsible for most of its typical side effects.

One of its notable side effects not commonly seen in clinical practice is peripheral oedema. This is evidenced by limited reports and studies available regarding these side effects. From the literature, the few reported cases have been described as acute, self-limiting and resolved on discontinuation of the medication. Oedema is not listed in the BNF as a side effect of oral olanzapine, but is 'common or very common' with long-acting injectable olanzapine, which further emphasizes the rarity of this side effect among patients taking oral olanzapine.

This paper aims to discuss a case report of dose-dependent, persistent bilateral pedal oedema in a patient on olanzapine.

1 | Case Discussion

We describe the case of a woman in her 50s admitted with paranoid and persecutory delusions regarding the police and her neighbours.

The patient also presented with self-neglect, lack of insight and physical aggression and was detained under Section 2 of the Mental Health Act.

She was later diagnosed with paranoid schizophrenia and started on aripiprazole depot 400 mg monthly, as she continued to decline oral medication and investigations.

Aripiprazole depot was continued for 4 months at 400 mg monthly (licensed maximum dose); however, following persistent psychotic symptoms while on admission, antipsychotic switched from aripiprazole to oral olanzapine, as the patient had become more receptive to oral medication. Olanzapine trialled with plans that it would also improve her mood, and increase her appetite, as patient reporting low appetite and low mood at the time.

A month after olanzapine commenced, sertraline was also added due to ongoing symptoms of low mood.

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Three months later, the patient was assessed to have partial improvement; however, was still noted to be experiencing some persecutory delusions, so olanzapine was increased to 7.5 mg.

Eight months after olanzapine initially commenced, the dose was further increased to 10 mg, and about a week later, the patient reported bilateral ankle swelling. No swelling was noted in other body parts.

Physical examination showed low blood pressure of 100/52 mmHg and a pulse rate of 74 beats per minute. No haemodynamic compromise was noted, and the rest of the cardiovascular examination was normal except for bilateral ankle swelling.

Investigations revealed FBC with a slightly decreased haemoglobin level of 111 (Ref: 115–160 g/L); electrolytes results were within the normal range (sodium: 138 mmol/L, potassium: 4.1 mmol/L, creatinine: 58 umol/L) and the rest of the blood investigations included thyroid function. Renal function, liver function, albumin levels, cortisol levels and lipid profile were all within normal limits. No scans or chest X-rays were completed, as no indications were noted at review.

The patient also reported a history of iron deficiency, anaemia; however, she had been treated with ferrous sulphate and subsequent results were reported to be normal.

Following this, the patient developed a few episodes of postural hypotension. There were also concerns of chronic weight loss secondary to self-neglect noted and a dietician was involved. There was a history of an eating disorder in childhood; however, no evidence of intentional weight loss or features of an eating disorder was observed at the time of review. Cortisol levels were also taken, and there was no evidence of Addison's disease.

No initial concerns were raised regarding olanzapine being a potential cause of oedema due to a history of transient leg swelling at the age of 20. Ongoing monitoring was instated with a review of other possible causes of oedema.

The patient was subsequently discharged to the community mental health team (CMHT), where during assessment and examination, significant bilateral pitting pedal oedema up to the knees was observed. The patient reported that since diagnosis oedema had progressively worsened and affected mobility.

Cardiovascular examination was also repeated revealing a sitting blood pressure of 102/76 mmHg and a heart rate of 78 beats per minute with no abnormal cardiovascular findings. The weight measured at the assessment was 66.3 kg and the height was 168.5 cm.

During the CMHT assessment, olanzapine was flagged as the likely offending agent, as no other causes were found. Investigation including FBC, renal function tests, liver function tests, thyroid function tests, vitamin B and folate levels, lipid profile and iron studies were completed. Investigation revealed borderline HBA1C results, but no other abnormalities that could explain oedema were observed.

Naranjo scale scoring (Naranjo scale is to assess the likelihood of a side effect being attributable to a specific drug) for our patient, was an 8, which put her in the probable range. Scores were not higher, as no blood levels of olanzapine had been taken and the patient had no previous history of olanzapine use. She was then diagnosed with olanzapine-induced pedal oedema.

Due to significant reduction in psychotic symptoms on olanzapine, frusemide commenced to manage oedema; however, this was not tolerated by the patient. As repeat investigations also revealed slightly deranged HBA1C, which was assessed to also be linked to olanzapine, the decision was made to discontinue olanzapine, and she was switched to flupentixol.

A month after olanzapine was discontinued, our patient reported a gradual reduction in oedema by 1 month and a detailed physical examination revealed complete resolution by 6 weeks.

Patient's weight was also noted to be 64.2 kg at 6 weeks, a loss of 2.1 kg likely from oedema resolution, as eating and lifestyle habits were not reported to have changed. Electrolytes results were within the normal range (sodium: 136 mmol/L, potassium: 4.12 mmol/L, creatinine: 60 umol/L). Other physical health observations and examinations were noted to be normal.

The patient's psychotic symptoms also remained stable on flupentixol with no significant side effects.

2 | Literature Search

Searches were done for relevant articles and case reports using the search words ‘Olanzapine, Pedal oedema’ and ‘Olanzapine, oedema’.

Searches were made using Google Scholar, PubMed, Cochrane Library and so forth and initially yielded about 473 results. Twenty-one reports were relevant to our review, but one was excluded as it was in Turkish and not translated.

Eventually, 20 reports were included in our review.

3 | Discussion

Olanzapine is a second-generation antipsychotic that exerts an antagonistic effect on serotonin 5HT2A/2C, 5HT6, dopamine D1-4, histamine H1 and adrenergic α1 receptors.

Premarketing trials report oedema as an infrequent side-effect noted in 3% of olanzapine-treated patients compared to 1% in Placebo.

While the mechanism of olanzapine-related oedema remains largely unclear, its effect in targeting multiple receptor types and subtypes offers some hypotheses.

Some literature suggests that this side effect is more prominent following the combination of olanzapine with other medications such as antidepressants [3]. The patient discussed in this report was

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also on a combination of sertraline and olanzapine, a common combination used in clinical practice.

Olanzapine-related oedema is often speculated to be a result of α1 adrenergic receptor blockade, as this may lead to vasodilation, decreased vascular resistance and fluid movement into the intravascular space. Other theories include H1 and 5HT-2 antagonism causing smooth muscle relaxation and potential oedema.

Presentation of olanzapine-induced oedema is also variable, as there have been reports of angioedema-type symptoms supported by histology [4, 5]. This also suggests that the mechanism of action is likely a combination of various aetiological factors.

4 | Clinical Relevance

4.1 | Time of Onset

Most published reports have given average timelines of developing oedema between a few days to months. In a study by Arslan, Bulut, and Naki [6], the patient was reported to have developed pedal and hand oedema within 2 days of an increased dose of 15 mg of olanzapine. This contrasts with another study by Malhotra and Shrivastava [7], where periorbital oedema was noted 7 months after commencing olanzapine.

Although the time of onset of oedema was noted to be wildly variable, most cases were observed within a month of starting olanzapine or increasing the offending dose. This is an indication of the need for a period of monitoring and a high index of suspicion when increasing doses.

4.2 | Dose-Dependence

A general observation regarding olanzapine-related oedema is that it can often be dose-dependent; in most of our identified case reports, oedema was observed in doses of 10 mg and above; however, in some of these cases, starting doses were the same as offending doses, making it difficult to ascertain the possibility of occurrence at lower doses. Despite this, it has been reported to occur at 2.5 mg, such as in the case report by Deshauer, Erwin, and Karagianis [8].

In the case we reported, the patient had no reports of oedema for months on lower doses of olanzapine, with symptoms only occurring after the dose was increased to 10 mg.

4.3 | Location

While pedal oedema was mostly reported either in isolation or in combination with swelling of other body parts, our review suggests that location is varied, and reports oedema in other areas such as pericardium [6], periorbital region [7, 9–11], face [12–14] and hands [8, 12, 15] and as described in this case report, Pedal/Pretibial oedema [4, 6, 8, 15–21].

A high index of suspicion is advised when examining for oedema related to olanzapine use, particularly when there is persistent unexplained oedema as in the case described by Herlihy, Duff, and Sadlier [13], where there was persistent facial oedema mimicking Morbihan disease, a condition characterized by chronic, persistent erythematous facial oedema.

4.4 | Time to Resolution

A significant difference observed in our case was the time to resolution of oedema. From the available literature, this ranges from 3 days to a month. In our patient, resolution was much slower, and it took 6 weeks, to achieve complete resolution.

As with the onset of symptoms, there is an observed variation in the time taken for symptoms to resolve. Surprisingly, in one of the observed cases [7], olanzapine withdrawal led to quick resolution within 3 days. This is compared to one of the cases reported by Umar and Abdullahi [15], where even with the addition of a loop diuretic and olanzapine withdrawal, resolution took 3 weeks. This also further buttresses theories regarding the varied pathophysiology and, subsequently, the remission of symptoms.

4.5 | Management

An essential aspect of this discussion is the management of this side effect, particularly in individuals whose symptoms have responded well to olanzapine.

Approaches include the use of antidiuretics, antihistamines, steroids, and, more commonly, the reduction in dose/withdrawal of olanzapine.

In our patient, frusemide was unfortunately not tolerated and withdrawal had to be done. The role of frusemide is observed to be varied; in reports by Cook, Shipman, and Fowler [3] and Umar and Abdullahi [15], frusemide was introduced to hasten the resolution of oedema following the withdrawal of olanzapine.

Deshauer, Erwin, and Karagianis [8] and Kumar Soni et al. described a concurrent use of frusemide and olanzapine, which led to the resolution of oedema but was noted to recur following the discontinuation of olanzapine. This suggests that in patients for whom there are limited antipsychotic options but experience side effects of oedema, the addition of long-term frusemide can be an option. However, this may present a need for other forms of monitoring, for example, electrolyte monitoring.

In one of the cases reported by Umar and Abdullahi [15], a reduction in dose from 20 to 10 mg led to the resolution of oedema.

Similarly, in another case by Tascon Cervera et al. [22], a reduction in dose to 10 mg led to the resolution of symptoms while managing psychiatric symptoms. This is in contrast to the case by Gopalakrishnan et al. where oedema persisted despite a reduction in dose from 5 to 2.5 mg. Overall, there is a case for

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maintaining lower doses if psychiatric symptoms are well controlled.

It is worthy of note that in most of the cases reviewed, olanzapine was either initially or eventually withdrawn, and this suggests that in the presence of other options to manage psychiatric symptoms, the withdrawal of olanzapine should be the most likely management choice.

Honma et al. and Williams et al. reported olanzapine-induced oedema with a presentation similar to angioedema. In these cases, antihistamines were also used in management, but these were also temporary measures as olanzapine was eventually discontinued.

5 | Conclusion

In conclusion, we have described a case of a middle-aged woman who developed significant bilateral pedal oedema on 10 mg of olanzapine. There continues to be limited data available regarding aetiology of the symptoms; however, close monitoring and a high index of suspicion are advised when commencing patients on olanzapine.

Consent

Verbal and written consent was provided by the patient to complete this case report.

Conflicts of Interest

The authors declare no conflicts of interest.

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