

Olanzapine-Induced Peripheral Oedema in a Pregnant Patient with Bipolar Affective Disorder

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Abstract

A number of medical conditions and medications can cause localized or generalized oedema. Bilateral peripheral oedema is infrequently described with olanzapine and is rarely seen as the side effect during pregnancy. A case of olanzapine-induced peripheral oedema in a 40 year old pregnant woman with a diagnosis of bipolar affective disorder is discussed. The exact mechanism of olanzapine to cause peripheral oedema is not known; a number of possible mechanisms are discussed. It is suggested that the clinicians should remain vigilant to promptly recognise this uncommon adverse reaction of olanzapine, which requires the discontinuation of the offending agent to reverse the adverse clinical event (German J Psychiatry 2013; 16(2): 84-86).

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Introduction

Various medical conditions and medications can cause both localized and generalized oedema. The medical conditions known to cause oedema include hepatic cirrhosis, lymphedema, nephrotic syndrome, glomerulonephritis, Graves' disease, congestive heart failure and hypo-proteinaemia (Braunwald, 2001; Powell & Armstrong, 1997). The medications that can potentially cause localised or generalised oedema include anti-hypertensives, steroids, non-steroidal anti-inflammatory and immunosuppressives (Chertow & Thibault, 1998).

Olanzapine is an atypical antipsychotic that has high affinity for serotonin (5-HT_{2A}, 5-HT_{2C}), dopamine (D₁₋₄) muscarinic (M₁₋₅), histamine (H₁), adrenergic (α ₁) receptors and weak affinity for β -adrenergic and GABA_A receptors (Stahl, 2000). While the common side effects of olanzapine are weight gain and somnolence; the less common side effects include dry mouth, dizziness, constipation, dyspepsia, and increased appetite (Martindale, 2005); akathisia, tremors and peripheral oedema are among the rare side effects. A case of olanzapine-induced peripheral oedema in a pregnant middle-aged patient with bipolar affective disorder is discussed here.

Case Report

Ms. A, is a 40-year-old white woman who was diagnosed with bipolar affective disorder, at the age of 28 and had received various anti-psychotics, anti-depressants and mood stabilizers in the past. Recently, she was admitted to the psychiatry ward as an involuntary patient due to a severe deterioration in her mental state which was triggered by non-compliance with her medication and disengagement from services. She was diagnosed to be suffering from bipolar affective disorder, current episode manic with psychotic symptoms (F 31.2).

On admission she presented with psychotic features, elation of mood, pressure of speech, aggressiveness, and threatening behaviour. Her psychotic features included delusion of persecution, delusion of grandeurs and delusion of reference. She talked about 'aliens and spaceships' and believed that she was bestowed with extraordinary healing power. She was agitated, racially abusive and sexually dis-inhibited and had to be transferred to psychiatry intensive care unit (PICU).

Ms. A had stopped misusing illicit drugs about 15 years ago but continued to drink alcohol in moderation. However she started drinking excessively, 5 or 6 units per day, a couple of weeks prior to her current admission. Ms. A had several episodes of bipolar affective disorder since 2002 and had few

admissions into psychiatry hospital both as a voluntary patient and under mental health act.

Ms. A was 16 weeks pregnant at the time of admission. Her pregnancy was not accompanied with any co-morbid physical health problem. She became pregnant twice in the past and both the pregnancies were uneventful. During her current admission she was assessed and regularly monitored by obstetrician and the possibility of pre-eclampsia was carefully ruled out.

The benefits of treating her current manic episode with antipsychotics far outweighed the risks of the use of antipsychotic during pregnancy. The decision to choose quetiapine and olanzapine during pregnancy was based on the studies suggesting that both quetiapine (McKenna et al., 2005; Tenyl et al., 2002; Taylor et al., 2003) and olanzapine (Patton et al., 2002; Ernst et al., 2002) are not primarily teratogenic in humans. Ms. A was, therefore, initially started on quetiapine 50 mg daily, which was gradually increased to 300 mg twice a day. However after a trial of 4 weeks, quetiapine was discontinued as it failed to produce any noticeable improvement and it was replaced with olanzapine 5mg a day. As she remained agitated, chaotic, dis-inhibited and aggressive, her olanzapine was build up to 10 mg twice a day. It was further increased to 15 mg twice a day as she remained unsettled. In addition to olanzapine, she was also started on a regular oral dose of lorazepam 2mg twice a day that was later replaced with diazepam 10 mg twice a day. Besides psychotropic medication, Miss A did not receive any other medications including diuretics and non-steroidal anti-inflammatory drugs (NSAIDs).

Four weeks after the commencement of olanzapine, Ms. A developed extensive bilateral pedal oedema and swellings in both her hands. Her fingers were so swollen that her ring in one of the fingers had to be cut. The swellings in hands, feet and ankles were soft, non-tender and pitting on pressure without any raised temperature. There was no evidence of any rash, skin thickening, ulceration or pigmentation.

Her physical examination including cardiac and respiratory examination was unremarkable. There were no signs of cardiac failure, pulmonary oedema, varicose or spider veins on the legs or ankles. Her blood pressure was recorded on different occasions and it was within the normal range. The results of chest X-ray, ECG, complete blood counts, liver-function tests, renal functions, electrolytes and thyroid function tests were normal. There was no evidence of proteinuria.

It was thought that her peripheral oedema was due to olanzapine. She scored 7 on the Adverse Drug Reaction (ADR) Probability Scale designed by Naranjo et al. (1981). Her olanzapine was discontinued and was replaced with chlorpromazine as she had responded well to chlorpromazine in the past and chlorpromazine is considered to be safe during pregnancy. Approximately 3 weeks after the discontinuation of olanzapine her oedema resolved completely. Her mental condition settled in about 6 weeks' time and she was discharged on chlorpromazine 800mg daily and diazepam 4mg twice a day. As she had a long history of poor engagement with the services, she was discharged on community treatment order (CTO) available in the UK. Periph-

eral oedema did not reappear during further follow up in the community. The haematological and biochemical investigations that included complete blood counts, liver-function tests, renal functions, electrolytes and thyroid function tests were within normal limits. Follow up with the obstetrician was uneventful and her delivery was without any complications.

Discussion

Peripheral oedema during pregnancy may be caused by increased volume of fluid in the body, hormones and growing uterus which places pressure on the veins. In the case presented here, the peripheral oedema was bilateral; it appeared after olanzapine was administered and disappeared when the offending drug was discontinued. The oedema started appearing when the patient was receiving a dose of olanzapine 20 mg daily. She scored 7 on the ADR Probability Scale, suggesting high probability of peripheral oedema to be due to the administration of olanzapine. The ADR Probability Scale is a 10 items scale to estimate the probability of an adverse clinical event to be a drug reaction.

A similar case of 50-year-old female patient, with bipolar affective disorder, has been described in the literature. She developed bilateral swelling in her hands and ankles two days after she was prescribed 2.5 mg of olanzapine. The oedema disappeared within a week of stopping olanzapine (Deshauer et al., 2006). Similarly another case of 58-year-old white male, with a diagnosis of bipolar disorder with psychotic features, has been reported who developed bilateral pedal oedema two months after the initiation of olanzapine. He was started on olanzapine 2.5 mg/day and was titrated to 10mg/day over the next 2 weeks. Two weeks after the discontinuation of olanzapine his pedal oedema completely resolved (Petkova & Yazel, 2000). However, in the case reported here, it took about 3 weeks for oedema to completely resolve. The relatively longer period to completely resolve the oedema could be due to its extensive level in this patient, although it is appreciated that the oedema should have resolved sooner after termination of olanzapine due to its short half-life and elimination from the body within few days. Premarketing trials of olanzapine have reported no significant differences regarding gender, time/dose, concomitant diagnoses or psychotropic medication. However, it was observed that there was a tendency for patients of older age and thyroid abnormalities to have a greater frequency of developing olanzapine induced oedema. In the oedema group, there was a positive correlation between age and severity (Ng et al., 2003).

A number of possible mechanisms have been suggested to explain the association between oedema and olanzapine. A relationship between dopaminergic antagonism and idiopathic oedema has been advocated (Braunwald, 2001; Franco et al., 1991; Norbiato et al., 1979; Dent & Edwards, 1979). It is postulated that dopamine may affect epithelial fluid resorption, natriuresis and renin-angiotensin system (Adir & Sznajder, 2003; Zeng et al., 2007). Another plausible explanation is an allergic reaction to olanzapine giving rise to

peripheral oedema as has also been proposed for ziprasidone-induced oedema (Ku et al., 2006). Neuroendocrine changes caused by the anti-psychotic medication and adverse interaction between olanzapine and diazepam can also give rise to oedema (Christensen, 2003). Olanzapine is known to react antagonistically with both α_1 - and α_2 -adrenergic receptors and cause a hypodopaminergic state by blocking dopamine receptors. Also, it is known to cause 5-HT₂ receptor blockade, which can explain the genesis of peripheral oedema induced by olanzapine (Van Kammen & Marder, 2000).

Since the precise explanation of olanzapine-induced peripheral oedema remains unclear, further research is warranted to understand this condition. The case report discussed here is expected to help the clinicians to be vigilant to identify this uncommon side effect that requires no intervention, except monitoring of oedema, once the causative agent has been removed.

References

- Adir Y, Sznajder JJ. Regulation of lung edema clearance by dopamine. *Isr Med Assoc J* 2003; 5: 47–50.
- Braunwald E. Edema. *Harrison's Principles of Internal Medicine* (15th Edition); New York, NY: McGraw-Hill 2001.
- Chertow GM, Thibault GE. Approach to the patient with edema. In: Goldman L, Braunwald E, eds. *Primary Cardiology*. Philadelphia, Pa:Saunders 1998.
- Christensen RC. Olanzapine-associated bilateral pedal edema. *J Clin Psychiatry* 2003; 64(8): 972.
- Dent RG, Edwards OM. Bromocriptine-responsive form of idiopathic oedema. *Lancet* 1979; 2: 355–356.
- Deshauer D, Erwin L, Karagianis J. Case Report: Edema related to olanzapine therapy. *Can Fam Physician* 2006; 52: 620–621.
- Ernst CL, Goldberg JF. The reproductive safety profile of mood stabilizers, atypical antipsychotics, and broad-spectrum psychotropics. *J Clin Psychiatry* 2002; 63 (Suppl. 4): 42-55.
- Franco K, Tamburrino M, Campbell N, Campbell N, Pentz J, Evans C. Dopaminergic activity and idiopathic edema. *Hosp Community Psychiatry* 1991; 42: 309–310.
- Ku HL, Su TP, Chou YH. Ziprasidone-associated pedal edema in the treatment of schizophrenia. *Prog Neuropsychopharmacol Biol Psychiatry* 2006; 30: 963–964.
- Martindale. *The Complete Drug Reference* (34th Edition). In: Clowers W, editor. Great Britain: Suffolk 2005.
- McKenna K, Koren G, Tetelbaum M, et al. Pregnancy outcome of women using atypical antipsychotic drugs: a prospective comparative study. *J Clin Psychiatry* 2005; 66: 444-449.
- Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA, Janecek E, Domecq C, Greenblatt DJ. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther* 1981; 30: 239 – 245.
- Ng B, Postlethwaite A, Rollnik J. Peripheral oedema in patients taking olanzapine. *Int Clin Psychopharmacol* 2003; 18: 57–59.
- Norbiato G, Bevilacqua M, Raggi U, et al. Effect of metoclopramide, a dopaminergic inhibitor, on renin and aldosterone in idiopathic oedema: possible therapeutic approach with levodopa and carbidopa. *J Clin Endocrinol Metab* 1979; 48: 37–42.
- Patton SW et al. Antipsychotic medication during pregnancy and lactation in women with schizophrenia: evaluating the risk. *Can J Psychiatry* 2002; 47: 959-965.
- Petkova SP & Yazel JJ. Olanzapine-induced bilateral pedal edema: a case report. *Follow Gen Hosp Psychiatry* 2000; 22 (4): 290-291.
- Powell AA, Armstrong MA. Peripheral edema (Review). *Am Fam Physician* 1997; 55: 1721-1726.
- Stahl SM. *Antipsychotic Agents. Essential Psychopharmacology* (2nd Edition); Cambridge University Press 2000.
- Taylor TM, O'Toole M, Ohlsen R, et al. Safety of quetiapine during pregnancy (letter). *Am J Psychiatry* 2003; 160: 588-589.
- Tenyl T, Trixler M, Keresztes Z. Quetiapine and pregnancy. *Am J Psychiatry* 2002; 159:674.
- Van Kammen DP, Marder SR. Serotonin-dopamine antagonists. In: Kaplan HI, Sadock BJ, eds. *Comprehensive Textbook of Psychiatry*, vol2. 7th Edition. Baltimore, Md: Williams & Wilkins; 2000:2455-2474.
- Zeng C, Zhang M, Asico LD, et al. The dopaminergic system in hypertension. *Clin Sci (Lond)* 2007; 112: 583–597.