CASE REPORT

Mirtazapine Induced Pitting Oedema: A Case Report

Sharvindan Subramaniam[1], Rohinie Chandran[1], Yee Chin Chai[2]

[1]Hospital Sultan Ismail, Ministry of Health, Malaysia
[2]Hospital Permai, Ministry of Health, Malaysia

Abstract

Mirtazapine is an antidepressant that is classified as a noradrenergic and specific serotonergic antidepressant (NaSSA). It is recommended as one of the first line antidepressants for the treatment of major depressive disorder (MDD). We herein report an unusual side effect of mirtazapine where a middle aged lady who suffered from bilateral non tender pitting oedema with swelling at the lower limbs and numbness over bilateral hands for more than one month since the commencement of mirtazapine. It resolved gradually upon cessation of medication. A score of 7 was done retrospectively for Naranjo scale. The exact mechanism and its frequency are not well known yet. A high awareness of its potential effects is important among prescribers in order to offer better treatment care to patients.

Keywords: Mirtazapine, Bilateral Lower Limbs, Pitting Oedema

Introduction

Mirtazapine is classified as a noradrenergic and specific serotonergic antidepressant (NaSSA) [1]. It is recommended as one of the first line antidepressants for treatment of major depressive disorder (MDD) [2]. Mirtazapine has a unique pharmacological profile. It is a potent antagonist at presynaptic alpha2-adrenoceptors and postsynaptic serotonin 5-HT_2 and 5-HT_3 receptors, which indirectly enhances 5-HT_{1A}-mediated serotonergic neurotransmission [3]. Its potent anti-histamine property is also particularly beneficial for MDD with prominent sleep problems [4]. Its common side effects includes increased appetite, weight gain, somnolence and lethargy [5, 6].

In our case report, we described a patient who developed bilateral non tender pitting oedema following initiation of mirtazapine which gradually subsided two weeks after stopping mirtazapine.

Case Report

Mrs. L, a 52-year-old housewife, presented to psychiatric team with low mood, anhedonia, helplessness, worthlessness, poor sleep, lethargy, poor appetite, weight loss with fearfulness and nervousness for a period of four months in August 2018. She also became socially withdrawn. There was

a significant decline in her function as a housewife. No presence of psychotic symptoms. There is no family history of mental illness or substance use. Premorbidly, she was a hardworking and responsible housewife. Stressors were identified when her husband was diagnosed with colon cancer stage IV, who had to undergo surgery requiring a stoma bag and chemotherapy. She experienced financial issues as her husband was unemployed due to his illness.

Mental state examination revealed a middle aged, thin built and poorly kempt lady. There was poor eye contact and rapport. Speech was coherent and relevant but minimal verbal output, in short phrases and was slow in response. Her mood was low and affect was restricted. She was alert and oriented. Her vital signs were stable. Systemic examinations were unremarkable. Blood investigations including full blood count, renal profile and liver function test were normal. She was diagnosed with major depressive disorder and treated with oral escitalopram 5mg ON.

Subsequently, she defaulted her treatment and presented with another episode of depression. She no longer responded to escitalopram, even though it was combined with sertraline and non-pharmacological approach such as counselling for stress management and coping skills. Hence, a decision was made to combine escitalopram with mirtazapine 30mg ON. Three weeks later, she returned for follow-up with improvement of her depressive symptoms. At the same time, she started to complain of bilateral finger numbness when doing house chores which was non-specific. No significant finding was elicited upon clinical examination. Reassurance was given and mirtazapine was further optimized to 45mg ON with decrement of escitalopram to 10mg ON. One week after dosage increment, she started to experience bilateral ankle swelling, which progressed to involve midthigh level within one month. It was pitting and non tender in nature, but greatly affected her daily life. Her lower limbs were extremely heavy and she could hardly ambulate freely. Besides that, all her fingers were swollen with a tingling sensation which caused her to have sleepless nights. Her marriage ring also could no longer fit into her finger. She could not grasp things with both her hands and could not cook. She went to seek consultation in primary care clinic but was told that no specific cause was identified. During the psychiatric clinic follow-up consultation, her complaint was noted. Blood investigations such as full blood picture, renal, liver and thyroid functions tests with urine microscopy examination were found to be normal.

Mirtazapine was offed as it was suspected to cause such adverse drug reactions (ADR) and escitalopram was optimised up to 10mg ON. The limbs oedema gradually subsided two weeks after stopping mirtazapine and she had regained her bilateral lower limbs and upper limbs functions.

Discussion

Oedema occurs when there is volume expansion of extracellular fluid or excessive fluid accumulation within the cells [8]. It can either result from excessive movement of fluid from the intravascular to interstitium or reduced movement of water from interstitial space into the capillaries or lymphatic vessels [8]. There are two types of oedema, namely localized or generalized oedema [9]. Localized oedema could be results of localized venous congestion or inflammation whereas generalized oedema usually is of systemic aetiologies such as kidney or heart failures, liver failure and Cushing syndrome [9], On the other hand,

oedema also could be further classified into hydrostatic oedema, vasogenic oedema and lymphoedema based on its different pathophysiology which could involve increased capillary hydrostatic pressure, decreased plasma oncotic pressure, increased capillary permeability or obstruction of the lymphatic drainage system [8]. As in this case report, the pitting oedema occurred as ADR of mirtazapine. When the pitting oedema resolved, we retrospectively assessed the patient based on Naranjo scale, a score of 7 signified probable ADR had occurred [7].

It is not uncommon that oedema happened to be an ADR of a particular medication. There is a wide range of medication that can result in oedema including antihypertensives (calcium channel blocker, beta blocker), antivirals (acyclovir), hormones (corticosteroid or sex hormone), chemotherapeutics (cyclophosphamide), cytokines (interleukin), nonsteroidal anti-inflammatory drugs (celecoxib), antidepressants, particularly monoamine oxidase inhibitors [10]. Moreover, there are several case reports on oedema as ADR of other psychotropic medication, such as risperidone [11], olanzapine [12], quetiapine [13], trazodone [14], pregabalin [15], escitalopram [16] and mianserin [17].

Pertaining to mirtazapine, there are several case reports on patients with similar side effects but differ individually. Saddichha (2014) and Lai et al (2016) have reported bilateral lower limb pitting oedema in female patients with complete resolution after mirtazapine was discontinued [18, 19]. There are two male patients who suffered from bilateral lower limb oedema associated with more serious symptoms including shortness of breath, anemia, fever, constipation and increased erythrocyte sendimentation rate [20, 21]. The range of dosage for those cases were within 30 to 60mg daily, but it was less severe in females as compared to males. As in this case, patient first complained of mild bilateral hand numbness after mirtazapine was added on to the treatment regime. This could be the early signs of oedema whereby expansion of interstitial spaces causing peripheral nerve compression [22]. As the numbness was not recognized earlier, it progressed into bilateral lower limb oedema with dose increment. The proposed mechanism involves interaction of alpha antagonism that causes vasodilation in smooth muscle and pooling of blood that results in localized vasogenic oedema [20]. However, the exact pathophysiology and whether the severity of its side effects differ in terms of gender is not well known.

Conclusion

The case illustrated above suggests that mirtazapine is the most likely cause of the pitting oedema. Even though it was not life-threatening to the patient, it has caused significant discomfort and suffering to the patient throughout her treatment with mirtazapine. Despite not knowing the exact pathophysiology of the development of oedema, awareness and early recognition by prescribers could offer better treatment care to patients who are suffering from ADR.

Acknowledgement

We would like to thank the Director General of Health Malaysia for his permission to publish this article.

We would like to record our appreciation to the patient for her consent to the writing of this case report, too.

Declaration

The authors report no actual or potential conflicts of interest.

The authors received no specific grants from any funding agencies.

References

[1] Kent JM. SNaRIs, NaSSAs, and NaRIs: new agents for the treatment of depression. Lancet. 2000;355(9207):911-8.

[2] Kennedy SH, Lam RW, McIntyre RS, Tourjman SV, Bhat V, Blier P, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) 2016 Clinical Guidelines for the Management of Adults with Major Depressive Disorder: Section 3. Pharmacological Treatments. Can J Psychiatry. 2016;61(9):540-60.

[3] De Boer T, Ruigt GS, Berendsen HH. The alpha2-selective adrenoceptor antagonist Org 3770 (mirtazapine, Remeron®) enhances noradrenergic and serotonergic transmission. Human Psychopharmacology 1995;10(S2):S107-18.

[4] Anttila SA, Leinonen EV. A review of the pharmacological and clinical profile of mirtazapine. CNS Drug Reviews. 2001;7(3):249-64.

[5] Chiu HW, Li TC. Rapid weight gain during mirtazapine treatment. The Journal of Neuropsychiatry and Clinical Neuroscience. 2011;23(1):E7.

[6] Watanabe N, Omori IM, Nakagawa A, Cipriani A, Barbui C, McGuire H, et al. Safety reporting and adverse-event profile of mirtazapine described in randomized controlled trials in comparison with other classes of antidepressants in the acute-phase treatment of adults with depression: systematic review and meta-analysis. CNS Drugs. 2010;24(1):35-53.

[7] Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA, et al. A method for estimating the probability of adverse drug reactions. Clinical Pharmacology & Therapeutics. 1981;30(2):239-45.

[8] Scallan J, Huxley VH, Korthuis RJ. Capillary Fluid Exchange: Regulation, Functions, and Pathology. San Rafael (CA): Morgan & Claypool Life Sciences; 2010. Chapter 4, Pathophysiology of Edema Formation. Available from: https://www.ncbi.nlm.nih.gov/books/NBK53445/.

[9] Casey G. Oedema: causes, physiology and nursing management. Nursing Standard. 2004;18(51):45-51.

[10] Trayes KP, Studdiford JS, Pickle S, Tully AS. Edema: diagnosis and management. Am Fam Physician. 2013;88(2):102-10.

[11] Yang HN, Cheng YM. Peripheral edema associated with risperidone oral solution: A case report and a review of the literature. Journal of Clinical Psychopharmacology. 2012;32(1):128-30.

[12] Yaluğ I, Ozten E, Tufan AE, Alemdar M, Cerit C. Bilateral pedal edema associated with olanzapine

use in manic episode of bipolar disorder: Report of two cases. Progress in Neuropsychopharmacology & Biological Psychiatry. 2007;31(7):1541-2.

[13] Roy K, Astreika V, Dunn JE, Biyyani RS. Quetiapine-induced peripheral edema. General Hospital Psychiatry. 2009;31(2):194-5.

[14] Barrnett JO, Frances AL, Kocsis JA, Brown RI, Mann JJ. Peripheral edema associated with trazodone: A report of ten cases. Journal of Clincal Psychopharmacology 1985;5(3):161-4.

[15] Gallagher R, Apostle N. Peripheral edema with pregabalin. CMAJ 2013;185(10):E506.

[16] Ravi PB, Ravishankar GM, Andrade C. Bilateral peripheral edema as a rare adverse effect of escitalopram. Indian Journal of Psychiatry. 2014;56(1):97.

[17] Gundogmus I, Ispir M, Algul A. (2017) Mianserin induced periorbital edema: a case report. Psychiatry and Clinical Psychopharmacology. 2017;27(1):96-8.

[18] Saddichha S. Mirtazapine associated tender pitting pedal oedema. Australian and New Zealand Journal of Psychiatry. 2014;48(5):487.

[19] Lai FY, Shankar K, Ritz S. Mirtazapine-associated peripheral oedema. Australian and New Zealand Journal of Psychiatry. 2016;50(11):1108

[20] Das R, Shankar PR, Dhungana K, Mirtazapine-Induced Lower Limb Oedema. Journal of Pharmacy Practice and Research 2005;35(4):310.

[21] Kutscher EC, Lund BC, Hartman BA. Peripheral edema associated with mirtazapine. Annals of Pharmacotherapy. 2001;35(11):1494-5.

[22] Thatte MR, Mansukhani KA. Compressive neuropathy in the upper limb. Indian Journal of Plastic Surgery: Official Publication of the Association of Plastic Surgeons of India . 2011;44(2):283-97.

Corresponding Author
Dr. Chai Yee Chin
Hospital Permai Johor Bahru,
Persiaran Kempas Baru,
Kempas Banjaran,
81200 Johor Bahru,
Johor, Malaysia
Tel: 07-2311000
Fax: 07-2366897

Email: yeeinchai@gmail.com