Duloxetine-induced hypertensive urgency in type 2 diabetes mellitus with diabetic neuropathy

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Abstract:
We present a case of hypertensive urgency in a diabetic patient with painful diabetic neuropathy on duloxetine treatment. The patient’s blood pressure was high after taking 1-day dose of duloxetine and the patient was diagnosed with hypertensive urgency. The patient was managed with labetalol, leading to reduction in blood pressure. The patient’s medication was switched to telmisartan and metoprolol, which leads to resolution of increased blood pressure. This case report is a possible case of hypertensive urgency after the initiation of duloxetine managed with antihypertensives and resolves with the discontinuation of the duloxetine.

Keywords:
Duloxetine, hypertensive urgency, painful diabetic neuropathy

Introduction
Duloxetine acts by inhibiting the selective reuptake of serotonin (5-hydroxytryptamine [5-HT]) and norepinephrine (NE) and is categorized as a selective serotonin and norepinephrine reuptake inhibitor (SNRI). Duloxetine acts by central pain inhibitory mechanisms, which is thought to be linked to its central nervous system (CNS) 5-HT and NE activity potential.[¹] Both 5-HT and NE have significant neurotransmission activities in the brainstem and spinal cord’s descending pain inhibitory pathways. Moreover, to decrease the peripheral transmission of pain signals to CNS, these neurotransmitters are thought to behave synergistically.[²] Here, we report a case of hypertensive urgency secondary use of duloxetine for painful diabetic neuropathy therapy and also discuss the appropriate clinical presentation and management. As the incidence of hypertensive emergency induced by duloxetine is uncommon, our goal is to increase awareness of this life-threatening adverse event. Till date, a single case report of duloxetine-induced hypertensive emergency has been published by Mermi and Atmaca.[³] US Food & Drug administration approved label mentions hypertensive crisis has a temporal relationship with duloxetine based on the individual safety case reports (ISCR). However, a causal relationship cannot be established.

Case Report
In June 2019, a 62-year-old female of middle socioeconomic strata, resident of rural area of Jodhpur, with a diagnosis of type 2 diabetes mellitus with hypertension (HTN), presented in AIIMS outpatient department with complaints of burning pain and numbness on both the legs and feet. She was on treatment with standard antidiabetic medication including insulin glargine and gliclazide. The patient was stabilized on amlodipine for HTN, rosuvastatin for hyperlipidemia, and aspirin for primary prevention of
cardiovascular diseases (CVD). Her BP was within normal limits and controlled with amlodipine. There was no history of alcohol intake or smoking. Diagnosis of painful diabetic neuropathy was made with the use of diabetic neuropathy symptom score and diabetes neuropathy examination score and she was enrolled in the randomized clinical trial entitled, “A Comparative Evaluation of Duloxetine and Gabapentin in Painful Diabetic Neuropathy,” and the Clinical Trial Registry of India (CTRI) number-CTRI/2018/10/015944. The patient was started on duloxetine 30 mg twice daily for over a period of 1½ month for painful diabetic neuropathy. Two days later, she presented in the emergency department with chief complaints of severe anxiety, nausea, and severe headache. There was no significant family history. There was a history of renal calculi 2 years back which was operated successfully. There was no history of chest pain, shortness of breath, palpitations, and abdominal or urinary complaints. There was no history of substance use and no history of labile HTN.

On examination, she was conscious and oriented. She was afebrile with pulse rate of 105 beats per min and blood pressure of 210/120 mmHg in supine position and with oxygen saturation of 93% on 2 L/min of oxygen flow. Other investigations such as liver function test and kidney function test were normal. 24-h urinary protein was 0.09 g/24 h, glycated hemoglobin was 9.2%, and low-density lipid cholesterol was 140 mg/dl. Arterial blood gases (ABG) were within normal limits. Laboratory and ABG findings are given in Table 1.

Hypertensive urgency secondary to the use of duloxetine was suspected and the patient was immediately transferred to the intensive care unit for surveillance and further management of blood pressure. Diagnosis of duloxetine-induced hypertensive urgency was made. Duloxetine was stopped and the patient was administered labetalol 20 mg by i.v. infusion. Her blood pressure decreased to 170/110 mmHg, and with repeated doses, it further declined to 154/88 mmHg, along with resolution of headache.

The patient improved clinically and symptomatically. She was administered oral telmisartan 40 mg for the control of BP and tablet metoprolol 25 mg once daily was also included in her treatment regime. She was discharged on the next day with tablet telmisartan 40 mg once daily, along with metoprolol 25 mg for control of BP and pantoprazole and domperidone for acid reflux. The reaction was reported to the World Health Organization Uppsala Monitoring Centre (WHO-UMC) through VigiFlow software (unique ID: INIPC: 2019–35052). The consent of the patient was taken for publication of her case report in scientific journal and she has no objection with the publication of information.

**Discussion**

This case illustrates a possible case of duloxetine-induced hypertensive urgency. Hypertensive urgency is acute, life-threatening emergency, associated with marked rise in blood pressure, usually above 180/120 mmHg without the presence of acute end-organ damage. Most patients suffering from hypertensive urgency and emergency have uncontrolled or unknown chronic HTN. However, the disease may occur in people who are normotensive.[4] Assessment of hypertensive urgency and emergency includes certain history and physical examination points to be emphasized. Medical history should include history of past treatment, ruling out illicit drug use, CVD, neurological symptoms, and urinary complaints. Information about known clinical and medical conditions, such as thyroid disorders, systemic lupus erythematosus, systemic sclerosis, Cushing’s syndrome, abdominal pain, dyspnea, and menstrual history, can be extremely helpful.

In general, blood pressure is reduced by approximately 10% in the 1st hour and fifteen percent over next 2-3 hours gradually. Anti hypertensive drug of choice includes labetalol, nicardipine, clevidipine, esmolol, fenoldopam, hydralazine, and phentolamine.

It has been observed that there is greater rise in mean systolic and diastolic blood pressure in patients on tricyclic antidepressants (TCA), which may increase the probability of stage I HTN.[5] The second-generation antidepressants such as selective serotonin reuptake inhibitors (SSRIs) and SNRIs are mainstay in the management of affective disorders such as anxiety, depression, and pain disorders such as neuropathic pain. Escitalopram results in a slight, but not clinically significant, reduction of BP, without dose–response effect.[4] Venlafaxine has also been reported to cause increase in BP. The probable cause of venlafaxine-induced HTN is the rise in NE concentrations and the increased peripheral noradrenergic neurotransmission. Sibutramine, an amphetamine-like SNRI, the probable mechanism of sibutramine-induced HTN in both normotensive and hypertensive patients, is the increased quantity of circulating NE in the body.

Use of Naranjo’s probability scale and WHO-UMC causality scale assessment indicated duloxetine as a possible cause of hypertensive urgency. The safe dose of duloxetine is 20 mg/day and should be slowly increased to maximum of 60 mg/day in single dose or divided every 12 h. Duloxetine was used at a higher dose of 120 mg/day for the management of diabetic peripheral
neuropathy. 120 mg dose is no more effective than 60 mg/day, but the side effects are very common at 120 mg/day dose. A study done by Derby et al., predicted that on administration of duloxetine, prehypertensive patients may become hypertensive, but predose blood pressure levels can help in prediction of such events.[6] Overall, the study data suggest that the administration of supratherapeutic dosages of duloxetine up to 200 mg twice daily is usually not associated with serious, clinically relevant adverse events such as hypertensive emergencies.[6]

In subjects with preexisting HTN, hypertensive emergency and urgency with duloxetine has been rarely reported. Henceforth, in subjects with risk factors like known case of HTN or CVD, blood pressure monitoring is recommended, especially during initial months of treatment.

Table 1: Laboratory findings and arterial blood analysis report

| Laboratory test                      | Results | Normal values |
|--------------------------------------|---------|---------------|
| RBC count (x10⁶/ul)                  | 4.4     | 4.1-5.1       |
| Platelet count (x10³/ul)             | 50      | 150-450       |
| Hb (g/dl)                            | 12      | 12.3-15.3     |
| Hematocrit (%)                       | 40      | 36.9 and 44.6 |
| WBC’s (cells/mcL)                    | 5500    | 4,500-10,000  |
| Mean corpuscular volume              | 85      | 80-96         |
| Sodium level                         | 138     | 135-145       |
| Potassium level                      | 3.9     | 3.6-5.2       |
| Lipid profile (Chol+TG+LDL-C+HDL-C) mg/dl | 220/195/42/139 | <200/150/100/40-60 |
| Arterial blood gases                 |         |               |
| pH                                   | 7.38    | 7.35-7.45     |
| Oxygen saturation (%)                | 95      | 94-100        |
| Bicarbonate level (mmol/L)           | 24.5    | 22-26         |
| PO₂ (mmHg)                           | 81      | 75-100        |
| PCO₂ (mHg)                           | 31      | 35-45         |

Chol=Total Cholesterol, TG=Triglyceride, LDL-C=Low-density lipid cholesterol, HDL-C=High-density lipid cholesterol, RBC=Red blood cell, Hb=Hemoglobin, WBC’s=White blood cell

It can be concluded that hypertensive urgency can be caused by duloxetine. Therefore, clinicians should be cautious of likelihood of duloxetine-induced hypertensive urgency and should be vigilant to diagnose and report the incident.

Declaration of patient consent
The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest
There are no conflicts of interest.

References
1. Yaksh TL. Pharmacology of spinal adrenergic systems which modulate spinal nociceptive processing. Pharmacol Biochem Behav 1985;22:845-58.
2. Zhuo M, Gehbart GF. Biphasic modulation of spinal nociceptive transmission from the medullary raphe nuclei in the rat. J Neurophysiol 1997;78:746-58.
3. Mermi O, Atmaca M. Duloxetine-induced hypertension: A case report. Turk Psikiyatri Derg 2016;27:67-9.
4. Hypertensive Emergencies: Uncontrolled Blood Pressure, Management of Hypertensive Emergencies. Available from: https://emedicine.medscape.com/article/1952052-overview. [Last accessed on 2019 Jun 11].
5. Licht CM, de Geus EJ, Seldenrijk A, van Hout HP, Zitman FG, van Dyck R, et al. Depression is associated with decreased blood pressure, but antidepressant use increases the risk for hypertension. Hypertension 2009;53:631-8.
6. Derby MA, Zhang L, Chappell JC, Gonzales CR, Callaghan JT, Leibowitz M, et al. The effects of supratherapeutic doses of duloxetine on blood pressure and pulse rate. J Cardiovasc Pharmacol 2007;49:384-93.