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Savella® (Milnacipran) Causing Elevated Normetanephrines

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INTRODUCTION

Pheochromocytoma and paraganglioma are neuroendocrine tumors that can cause hypertension, anxiety, and palpitations, and are considerations in the evaluation of secondary causes of hypertension.[1] Medications used to control mood disorders, especially selective serotonin and norepinephrine reuptake inhibitors (SNRIs), specifically venlafaxine, can mimic such neuroendocrine tumors both biochemically, through elevations in normetanephrine levels, and clinically, through elevations in blood pressure and heart rate.

SNRIs increase the activity of serotonin and norepinephrine in the brain. Milnacipran HCl (Savella®) is an SNRI that is indicated for the management of fibromyalgia in adults; it is not indicated for management of depression, although the drug is chemically similar to other SNRIs used in treating depression.[2] Recent studies, however, have demonstrated the efficacy of milnacipran in the treatment of major depression.[3-5] In contrast with venlafaxine and duloxetine, which have a higher affinity for serotonin than for norepinephrine receptors, milnacipran has a balanced ratio of potency in the inhibition of norepinephrine and serotonin uptake.[6] Adverse effects of milnacipran most commonly include nausea (37%), headache (18%), constipation (16%), hot flush (12%), and insomnia (12%).[7,8] Other side effects of serotonin syndrome and increased suicidal behavior, especially in the young age group, are similar to antidepressants of the same class.

We describe a patient with resistant hypertension on milnacipran. This case revealed the relationship between milnacipran use and hypertension through elevation of catecholamines.

CASE REPORT

A 64-year-old female with uncontrolled hypertension, type 2 diabetes, and hyperlipidemia was seen in the endocrinology clinic after her primary care physician raised a question of a possible pheochromocytoma. Her symptoms had gotten worse over a period of five years and included palpitations, hyperhidrosis, headaches, anxiety, and dizziness with standing. The patient had been taking milnacipran for several years for the treatment of severe fibromyalgia.

Prior to this presentation, she had a five-year work-up for secondary causes of hypertension after holding milnacipran for a few weeks, including aldosterone to renin ratio and thyroid function tests; all results were normal (Table 1). She had a modestly elevated 24-hour urine for normetanephrines at 1381 with normal urinary metanephrines (Table 1). A clonidine suppression test was normal, with a suppression rate greater than 50%. CT of the abdomen and pelvis was unremarkable.

Repeat studies in the endocrinology clinic, while she was on milnacipran, revealed elevated plasma normetanephrine as well as elevated 24-hour urine norepinephrine and normetanephrines with the other labs unremarkable (Table 1). After these lab results, a metaiodobenzylguanidine (MIBG) scan and CT scan of the abdomen and pelvis showed no evidence of pheochromocytoma. Therefore, a PET scan was obtained as a localization study for a pheochromocytoma or a paraganglioma; the scan came back negative. It was concluded that, in the setting of normal PET, CT, and MIBG scans, the likely source of elevated normetanephrines, and probable cause of worsening hypertension, dizziness, palpitations, and sweating was milnacipran.

DISCUSSION

Serotonin norepinephrine reuptake inhibitors commonly are prescribed as therapy for depression and for fibromyalgia.[9,10] The three SNRIs approved in the United States are venlafaxine, duloxetine, and milnacipran. Although venlafaxine and duloxetine have a 30- and 10-fold selectivity, respectively, for serotonin, milnacipran is nonselective in blocking the uptakes of norepinephrine and serotonin.[11] In our case, a neuroendocrine tumor (e.g., a pheochromocytoma or a paraganglioma) was ruled out through serology and imaging. Specifically, CT scanning has a sensitivity of greater than 93% in the detection of pheochromocytomas and a specificity of 95% in the diagnosis of these tumors.[12] Whereas for MIBG, sensitivity is 86 - 90% for pheochromocytomas (especially in extra-abdominal tumors); specificity is as high as 99% with I-MIBG and is higher with I-MIBG (90% sensitivity, 100% specificity).[12,13] CT of the abdomen and MIBG showed no evidence of pheochromocytoma in our case. In addition, PET scan has 78% sensitivity for nonmetastatic pheochromocytomas and 76% sensitivity for metastatic pheochromocytomas, and is considered the best means of localizing primary pheochromocytomas and ruling out metastases.[12] The PET scan was negative in our case.

Table 1. Labs obtained by primary care and endocrinology.

Labs	First Set	Second Set
Plasma Norepinephrine	590 (ref 0-874)	
Plasma Epinephrine	29 (ref 0-62)	
Plasma Dopamine	< 30 (ref 0-48)	
Urine Normetanephrine	502	
24-hour Urine Normetanephrine	**1381 (ref 82-500)**	**2251 (ref 82-500)**
Urine Metanephrine	33	
24-hour Urine Metanephrine	91 (ref 45-290)	81 (ref 45-290)
Urine Epinephrine	1	
24-hour Urine Epinephrine	3 (ref 0-20)	6 (ref 0-20)
Urine Norepinephrine	60	
24-hour Urine Norepinephrine	78 (ref 0-135)	**165 (ref 0-135)**
Urine Dopamine	131	
24-hour Urine Dopamine	360 (ref 0-510)	74 (ref 0-510)
24-hour Urine Free Cortisol	11 (ref 0-50)	
Free T4	1.22 (ref 0.7-1.71)	
Total T3	156 (ref 80-181)	
TSH	1.263 (ref 0.4-4)	1.418 (ref 0.35-5)
Plasma Metanephrine		< 0.2 (ref < 0.5)
Plasma Normetanephrine		**1.2 (ref < 0.9)**
24-hour Urine VMA		4 (ref 0-7.5)
24-hour Urine Creatinine	1189 (ref 500-2000)	1340 (ref 500-2000)

Patients generally tolerate SNRIs well and milnacipran has an excellent cardiovascular safety profile with little effect on electrophysiologic values.[13,14] Clinical investigators have documented very modest increases in heart rate (3 - 5 beats/min) and systolic pressure (1 - 3 mmHg) in study subjects who took 100 to 200 mg of oral milnacipran daily. In rare instances, however, oral milnacipran has caused significant and sustained hypertension and tachycardia,[9,10] which appeared to occur in our patient. Intravenous milnacipran has increased heart rate significantly (by approximately 19% in the first 50 minutes) and systolic blood pressure (by approximately 21% in the first 10 minutes).[14] For instance, one patient with manic-depressive psychosis who took 100 mg/d of oral milnacipran developed a hypertensive response (blood pressure, 160/100 mmHg)[1]; another patient who took 150 mg/d of milnacipran developed severe hypertension, but his blood pressure fell to acceptable levels when the dose was reduced to 100 mg/d.[15]

One randomized study revealed that fibromyalgia patients receiving milnacipran had mean increases in blood pressure, both systolic and diastolic, by 4 - 5 mmHg, and heart rate by 13 - 14 bpm.[16] On the other hand, in a three year study of milnacipran for the treatment of fibromyalgia which included 1227 patients, clinically significant increases in blood pressure or heart rate occurred in ≤ 1.1% of patients, whereas nausea (25.9%) and headache (13.4%) were the most common events.[17] There also were increases in supine blood pressure (+4/3 mmHg) and heart rate (+5 bpm).[17]

The proposed mechanism of hypertension from SNRIs is increased vascular resistance, mediated by increased noradrenergic neurotransmission secondary to greater availability of norepinephrine at the postjunctional receptor.[1] This increase in noradrenergic neurotransmitters associated with SNRIs is supported further in a case of Tako Tsubo cardiomyopathy which was reported in a patient after an overdose of the SNRI, venlafaxine.[18] In that case, the urinary collection showed an elevated norepinephrine of 122 µg/24 h (normal level < 100 µg/24 h), comparable to our case, indicating that milnacipran can be associated with this noradrenergic response manifested by worsening hypertension, tachycardia, palpitations, and dizziness.

In another prospective study, plasma normetanephrine levels were increased in four patients receiving either venlafaxine or desvenlefaxine, including one patient with a level of 8800 pmol/L,[19] which further reinforces the correlation between the SNRI, specifically milnacipran in our case, and elevated catecholamines, namely normetanephrines. In one study comparing milnacipran to selective serotonin reuptake inhibitors (SSRIs) for major depression management, milnacipran was associated with a higher incidence of headache, dry mouth, and dysuria,[3] with our patient presenting with complaints of headaches and dry mouth. The tolerability of milnacipran was comparable to that of the SSRIs, with a higher incidence of dysuria with milnacipran, and a higher frequency of nausea and anxiety with the SSRIs.[4] Milnacipran may offer clinical advantages over tricyclic antidepressants (TCAs) in terms of tolerability, and over SSRIs in terms of efficacy. In particular, the lack of cardiovascular adverse events appears to offer advantages in cases of deliberate overdose.[5]

Our case confirmed that elevated normetanephrine levels do not always indicate the presence of pheochromocytoma/paraganglioma and illustrated that milnacipran use, in particular, can mimic the symptoms of these neuroendocrine tumors. A similar finding was mentioned in a study by Neary et al.[20] which concluded that before blood is drawn to measure catecholamine levels, patients should discontinue all medications that could interfere with the results. SNRIs, such as venlafaxine (Effexor®), historically, and milnacipran (Savella®), as described in our case, could interfere with elevations in neuroendocrine hormones and may contribute to worsening blood pressure, dizziness, sweating, and palpitations. Therefore, the patient was switched to another antidepressant that did not affect these hormones and, more recently, the patient reported significant improvement in her headaches, palpitations, and dizziness and her blood pressure has been within normal limits.

Keywords: milnacipran, serotonin and noradrenaline reuptake inhibitors, catecholamines, hypertension, pheochromocytoma

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