



L-type calcium channel blockers and a symptom complex mimicking de Melo-Souza's syndrome

Upinder Kaur¹ · Pritam Das² · Indrajeet Singh Gambhir² · Sankha Shubhra Chakrabarti³

Received: 22 August 2018 / Accepted: 23 November 2018 / Published online: 1 December 2018
© Fondazione Società Italiana di Neurologia 2018

Dear Editor,

Drugs are an important cause of tremor in the elderly and the second most common cause of Parkinsonism. Common medications which induce tremor include salbutamol, theophylline, valproate, anti-depressants, anti-psychotics, and anti-dopaminergics [1, 2]. The T-type calcium channel blockers (CCBs), cinnarizine and flunarizine, are classically associated with a syndrome known as the “de Melo-Souza's syndrome,” or flunarizine-cinnarizine-induced Parkinsonism (FCIP) [3, 4]. FCIP is diagnosed in a patient on these drugs, with any two of tremor, hypokinesia, rigidity, and postural instability. In its classic form, it mimics idiopathic Parkinson's disease. The syndrome is often associated with depression and other features may include anxiety, insomnia, decreased facial expression, decreased deep tendon reflexes, and generalized weakness. Older females are the usual victims and the symptoms resolve following discontinuation of the concerned CCB [3, 4]. We present the case of an elderly female with partly similar manifestations after exposure to the L-type calcium channel blockers nifedipine and amlodipine.

Case report

A 74-year-old hypertensive female presented with nausea and vomiting of 3 days duration. She had been diagnosed as a case of syndrome of inappropriate anti-diuretic hormone secretion (SIADH) with vitamin D deficiency, 15 days back and was put on telmisartan 40 mg/day, amlodipine 5 mg/day, tolvaptan 15 mg/day, metoprolol 12.5 mg/day, vitamin D and calcium supplements, and clonazepam and paracetamol on an as needed basis. Five days back, she had visited the out-patients' clinic with tremulousness of bilateral upper and lower limbs and a tendency to fall (VIDEOS 1A and 1B). She was diagnosed with essential tremor and depression for which long acting propranolol 40 mg/day and amitriptyline 10 mg/day were started. Amlodipine was discontinued considering a possible association with tremor and telmisartan dose was increased to 80 mg/day. At the present visit, the movements had subsided. The patient was afebrile, her Glasgow Coma Score was 15 (E4V5M6), blood pressure was 160/90 mmHg, pulse rate was 84/min, and bilateral lung fields were clear. Routine investigations were within normal limits except for serum sodium which was low (Table 1). Workup for hyponatremia (Table 1) led to a diagnosis of SIADH, which the authors presumed to be due to amitriptyline. Amitriptyline was tapered, and free water restriction was started. Tolvaptan was added at 15 mg/day from day 2 and serum sodium started improving from day 3. Since her blood pressure increased to 190/110 mmHg on day 5, oral sustained release nifedipine 20 mg b.i.d was started. The patient developed tremor of bilateral upper and lower limbs, difficulty in walking without support, and a tendency to fall, within 1 day of nifedipine initiation. These movements were present at rest as well as were postural. Rigidity, hypokinesia, sialorrhoea, behavioral abnormalities, and autonomic fluctuations were absent. The patient was conscious and oriented and the neurological examination apart from the tremor was unremarkable. Propranolol dose was increased to 80 mg/day but without improvement. Since tremor had previously been suspected

Electronic supplementary material The online version of this article (<https://doi.org/10.1007/s10072-018-3662-1>) contains supplementary material, which is available to authorized users.

✉ Sankha Shubhra Chakrabarti
sankha.geriatrics@gmail.com

¹ Department of Pharmacology, Institute of Medical Sciences, Banaras Hindu University, Varanasi, UP, India

² Department of General Medicine, Institute of Medical Sciences, Banaras Hindu University, Varanasi, UP, India

³ Department of Geriatric Medicine, Institute of Medical Sciences, Banaras Hindu University, Varanasi, UP, India

Table 1 Biochemical, hematological, and radiological investigations

Investigations	Previous hospital visit day 1	Previous hospital visit (discharge)	Present hospital visit day 1	Present hospital visit day 4	Present hospital visit day 10
Hb (g/dL)	10.2			11.8	
TLC (/ μ L)	9500			9920	
DLC (%)	N67L22M9E2			N72L21M5E1	
PC (10^5 / μ L)	2.6			3.8	
MCV (fL)	85			88	
Cr/urea (mg/dL)	0.5/22			0.8/35	0.8/33
TB/DB (mg/dL)	0.5/0.2				0.6/0.2
SGOT/SGPT (U/L)	8/19				23/18
TP/Alb (g/dL)	6.8/4.1				7.7/4.2
Serum Na/K (mmol/L)	115/3.6	128/4	112/3.6	122/3.56	129/3.9
S. uric acid (mg/dL)	1.1		1.7		
Urinary Na/K (mmol/L)	112/19		99/32		
S. Ca/PO4 (mg/dL)	8.6/2.2				
RBS (mg/dL)	109		126		
pH	7.4	7.4	7.4	7.4	7.5
Ionic Ca (mmol/L)	0.96	1.1	0.98	1.12	1
PCO ₂ (mm Hg)	34.4	33	31.6	30.6	35
S. HCO ₃ (mmol/L)	23	24	23.7	22	25
T3/T4/TSH	61 /13/2.2				
USG abdomen	Normal		Normal		
2-D echocardiography	Grade 1 diastolic dysfunction				
NCCT head	Within normal limits of age				
MRI brain					Within normal limits of age

Hb, hemoglobin; TLC, total leukocyte count; DLC, differential leukocyte count; PC, platelet count; MCV, mean cell volume; Cr, creatinine; SGOT, serum glutamate oxalate transaminase; SGPT, serum glutamate pyruvate transaminase; TB, total bilirubin; DB, direct bilirubin; TP, total protein; Alb, albumin; TSH, thyroid stimulating hormone; MRI, magnetic resonance imaging; NCCT head, non-contrast computed tomography scan of head; USG, ultrasound

to occur with amlodipine, nifedipine was discontinued, presuming a class effect. Complete disappearance of the tremor occurred within 24 h. Clonidine and metoprolol were added for blood pressure control. On a review of the past medical records, the patient was found to have developed similar tremor during her first hospital stay 15 days back, with use of nifedipine-atenolol combination.

Essential tremor had been suspected initially but failure to respond to propranolol and a plausible temporal relationship of appearance and disappearance of tremor with amlodipine and nifedipine made this diagnosis unlikely. Tremor is less often a manifestation of hyponatremia but more so a consequence of rapid correction of hyponatremia, which may result in osmotic demyelination syndrome. The latter usually presents days after serum sodium levels have normalized and comes in the form of dysphagia, dysarthria, flaccid quadriplegia, mental confusion, and sometimes tremor when the basal ganglia is involved [5]. Tremor of extrapyramidal

myelinolysis does not disappear within 1 day opposed to what was observed in this case after discontinuation of CCB. However, keeping this diagnosis in consideration, magnetic resonance imaging of the brain was performed using a Siemens Magnetom Avanto 1.5 Tesla machine with routinely employed T1, T2, FLAIR, and diffusion-weighted image sequences in axial plane and a T1 sagittal image. No evidence of vascular damage, osmotic demyelination, or other abnormalities were found. Vascular Parkinson's syndrome was also ruled out in the process. On applying the Naranjo scale of causality association, the score came out to be 6 which suggested a "Probable" association with CCBs. Hence, a final diagnosis of CCB-induced tremor was made, and family members were cautioned against future use of this drug class. The patient was finally discharged after adequate control of blood pressure. She has been on follow-up for 14 months and has never shown signs of depression or tremor (VIDEO 2 at 1-month follow-up).

Discussion

Tremor may be disabling and may adversely affect the quality of life. The authors have presented an atypical case of an elderly hypertensive female who developed drug-induced tremor, a tendency to fall, and depressive features after exposure to two different members of the dihydropyridine class of calcium channel blockers. Furthermore, though our patient did not demonstrate hypokinesia or rigidity, the remaining clinical presentation shares significant resemblance with FCIP/de Melo-Souza's syndrome classically described with flunarizine and cinnarizine [3, 4]. Table 2 shows clinical features present in our patient and those in FCIP, described in detail by de Melo-Souza in 1989 [3, 4]. Our patient also received telmisartan and amitriptyline before and during hospitalization and tolvaptan, metoprolol, and clonidine during hospital stay. The patient's involuntary movements subsided while she continued to be on metoprolol, telmisartan, amitriptyline, tolvaptan, and clonidine. The most definite temporal relationship existed between CCB use and tremor. The weight of past evidence too was in favor of this group. There are many case reports of CCB-induced hyperkinetic disorders. Nifedipine has been linked to myoclonus and myoclonic dystonia [6]. Likewise, there are few reports of amlodipine-induced myoclonus and tardive dystonia [7, 8]. A recent study by Munhoz and others on reversible drug-induced Parkinsonism showed a variability of manifestations depending on the culprit drug-class. The CCBs were one of two major drug classes responsible and demonstrated a longer duration of symptoms and higher tremor scores [9].

Tremor is differentiated from myoclonus only based on rhythmicity, and often in case of tremor of variable amplitude, naked eye examination is unable to differentiate the two [10]. The authors considered the involuntary movements in the current case to be drug-induced tremor.

How calcium channel blockers may result in Parkinsonian features is uncertain, but many hypotheses exist. Both amlodipine and nifedipine can cross the blood-brain barrier [11]. The L-Ca 1.3(v) calcium channels are present on the neurons of substantia nigra and play a pacemaking role in neuronal function [12]. This subtype of calcium channels is thought to positively regulate tyrosine hydroxylase and dopa decarboxylase enzymes. They are upregulated in aged neurons and are thought to increase the aging-related oxidative stress in the substantia nigra, thereby contributing to Parkinsonism. Blockade of such channels by calcium channel blockers like isradipine is being investigated with enthusiasm as a potential disease-modifying option for Parkinsonism [13]. We hypothesize another implication of the presence of such calcium channels. It is possible that the same channels if blocked can produce an acute decline in dopamine levels in neurons of the substantia nigra. In a way, this differential effect of isradipine on one side and amlodipine/nifedipine (also dihydropyridines) on the other would be like the dual role played by dopamine in Parkinson's disease, where a deficiency of dopamine is responsible for symptoms while dopamine is also involved in oxidative neurotoxicity in the long run. Another possibility is the non-selective blockade by dihydropyridines, of presynaptic calcium channels

Table 2 A comparison of the clinical features of FCIP and the current case

FCIP	Present case
Parkinsonism diagnosed after therapy with either flunarizine or cinnarizine (at least two of the cardinal signs of Parkinsonism: bradykinesia, rigidity, postural instability, and resting tremor)	Symptoms after therapy with amlodipine/nifedipine
Rigidity	✗
Tremor	Involuntary movements
Postural instability	✓
Bradykinesia	✗
Associated other features	
Depression	✓
Insomnia	✗
Anxiety	✓
Facial hypomimia	✗
Impaired motor coordination	✓
Weakness	✓
Mainly affects elderly patients, particularly females	✓
Remission of Parkinsonian symptoms after discontinuation of flunarizine or cinnarizine	Remission thrice; each time after withdrawal of nifedipine or amlodipine
Other causes of Parkinsonism (including drugs that can cause movement disorder) excluded by clinical history and neurological examination	Vascular etiology, myelinolysis involving the basal ganglia, metabolic causes, and common drugs causing such symptoms ruled out. Temporal relationship present with CCBs on all three occasions

CCB, calcium channel blocker

resulting in decreased dopamine release, as has been suggested to be a possible mechanism in the FCIP pathogenesis [4]. These mechanisms however need experimental verification. The authors suggest a role of calcium channels of different types in the basal ganglia and the potential contribution of these channels to the pathogenesis of diverse types of tremor.

Funding support Elderly Pharmacovigilance Programme has funding support from the National Programme for Healthcare of the Elderly, Ministry of Health and Family Welfare, Government of India.

Compliance with ethical standards

Conflict of interest The authors declare that there is no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Elderly Pharmacovigilance Programme has the institutional ethics committee approval no. Dean/2015-16/IEC/411.

Informed consent Written informed consent was taken from patient's legal guardian (son) for publication of case and videos.

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

References

- Zádori D, Veres G, Szalárdy L, Klivényi P, Vécsei L (2015) Drug-induced movement disorders. *Expert Opin Drug Saf* 14(6):877–890
- Chen JJ (2012) Drug-induced movement disorders. *Mental Health Clin* 1(7):167–173
- Teive HA, Munhoz RP, Ferraz HB (2009) Flunarizine and cinnarizine-induced Parkinsonism: 25 years of de Melo-Souza's syndrome. *Arq Neuropsiquiatr* 67(3B):957
- Teive HAG, Troiano AR, Germiniani FMB, Werneck LC (2004) Flunarizine and cinnarizine-induced Parkinsonism: a historical and clinical analysis. *Parkinsonism Relat Disord* 10:243–245
- Martin RJ (2004) Central pontine and extrapontine myelinolysis: the osmotic demyelination syndromes. *J Neurol Neurosurg Psychiatry* 75:iii22–iii28
- Pedro-Botet ML, Bonal J, Caralps A (1989) Nifedipine and myoclonic disorders. *Nephron* 51:281
- Dressler D (2014) Tardive dystonic syndrome induced by the calcium-channel blocker amlodipine. *J Neural Transm* 121:367–369
- Wallace EL, Lingle K, Pierce D, Satko S (2009) Amlodipine-induced myoclonus. *Am J Med* 122:e7
- Munhoz RP, Bertucci FD, Teive HAG (2017) Not all drug-induced Parkinsonism are the same: the effect of drug class on motor phenotype. *Neurol Sci* 38:319–324
- Abdo WF, Van De Warrenburg BP, Burn DJ, Quinn NP, Bloem BR (2010) The clinical approach to movement disorders. *Nat Rev Neurol* 6:29–37
- Uchida S, Yamada S, Nagai K, Deguchi Y, Kimura R (1997) Brain pharmacokinetics and in vivo receptor binding of 1, 4-dihydropyridine calcium channel antagonists. *Life Sci* 61:2083–2090
- Surmeier DJ (2009) A lethal convergence of dopamine and calcium. *Neuron* 62:163–164
- Swart T, Hurley MJ (2016) Calcium channel antagonists as disease-modifying therapy for Parkinson's disease: therapeutic rationale and current status. *CNS Drugs* 30:1127–1135