

CASE REPORTS

Amlodipine causing symptomatic bradycardia in a healthy 71-year-old male

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ABSTRACT

Amlodipine is a calcium channel blocker that is well known to be vasoselective, thereby having minimal effects in cardiac tissue. However, recent literature have reported cases of symptomatic bradycardia associated with amlodipine use. We present a case of an otherwise healthy 71-year-old male who was found to have symptomatic bradycardia while taking amlodipine. He underwent comprehensive evaluation including an exercise stress echocardiogram during which he demonstrated chronotropic competence. Amlodipine was discontinued with return of his heart rate to baseline levels after 24 hours. There is a very low reported incidence of amlodipine-induced bradycardia (0.89% of cases). Despite its infrequency, it is important to recognize amlodipine-induced bradycardia as simply discontinuing the drug will lead to complete resolution of symptoms. Failure to recognize this side effect may lead to unnecessary healthcare costs and negatively impact patient outcomes.

Key Words: Amlodipine, Symptomatic bradycardia, Calcium channel blockers

1. INTRODUCTION

Amlodipine is a widely used dihydropyridine (DHP) L-type calcium channel blocker (CCB) that is not commonly known to cause bradycardia due to its vasoselectivity. In fact, literature published shortly after its release in 1990 claimed that it does not cause bradycardia.^[1,2] However, in recent years, there has been an increasing number of cases reporting that amlodipine is indeed associated with significant symptomatic bradycardia.^[3] In 2010, Ramadan and Quyyumi from Emory University School of Medicine reported a case of persistent bradycardia in a 42-year-old woman with associated dizziness, confusion, and fatigue for 1 month while taking amlodipine 10 mg daily. The patient had occasional periods of normal heart rate with exertion, which suggested chronotropic competence. Amlodipine was discontinued with complete resolution of her symptoms and normalization of her heart rate within 48-72 hours. Here, we present a

similar case of an otherwise healthy 71-year-old male who developed symptomatic bradycardia while taking amlodipine.

2. CASE PRESENTATION

Our patient was a 71-year-old Caucasian male with a medical history of only recently diagnosed hypertension. He presented to his primary care provider with a several week history of worsening fatigue and weakness that was associated with shortness of breath, intermittent palpitations, and postural dizziness. He was initially started on amlodipine 5 mg daily and was increased to 10 mg daily a few weeks prior to admission. He noted that his symptoms seemed to worsen after this dose increase. He took no other medications. He reported a low blood pressure of 109/69 mmHg on his home blood pressure cuff on the day of presentation. The patient was an athletic male who frequently runs up to

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4 miles a day. He followed an exercise regimen of 1 hour of cardio exercise 3 days a week and yoga on the remaining days. He reported that his resting heart rate is normally around 60 bpm. Although he had no personal history of heart disease, he had a family history of heart disease. He denied

any history of tobacco smoking or alcohol use. In his primary care provider's office, his heart rate was 44 bpm so he was advised to present urgently to the emergency department for further evaluation.

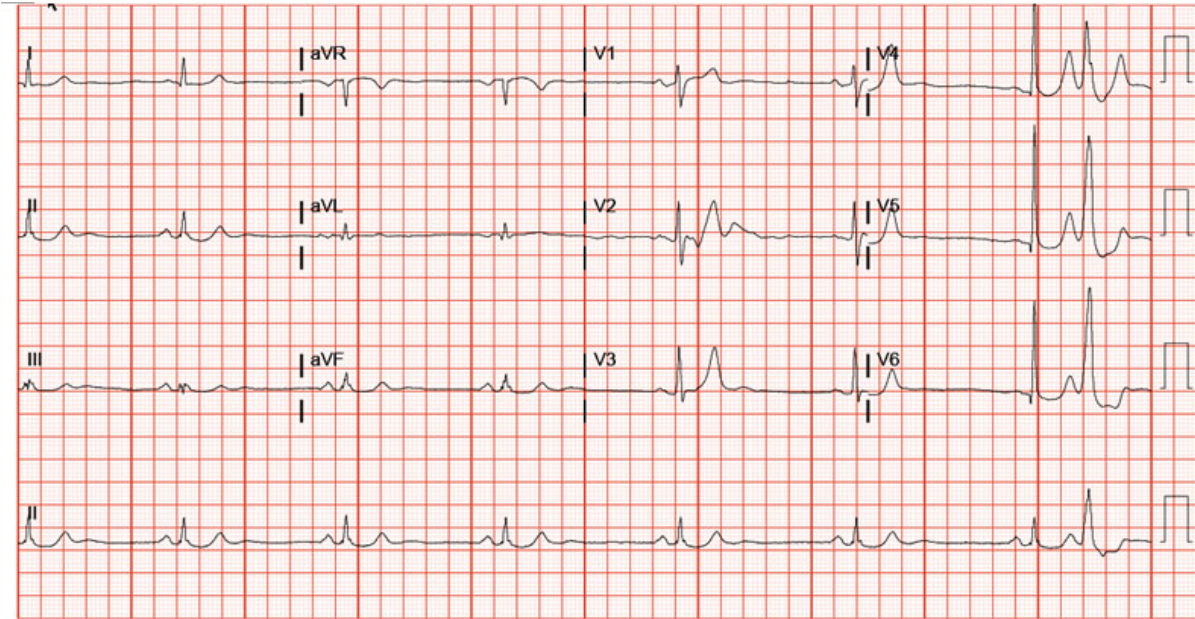


Figure 1. Initial ECG. This ECG was taken upon the patient's arrival to the emergency department. It shows sinus bradycardia at a heart rate of 44 bpm with occasional PVCs

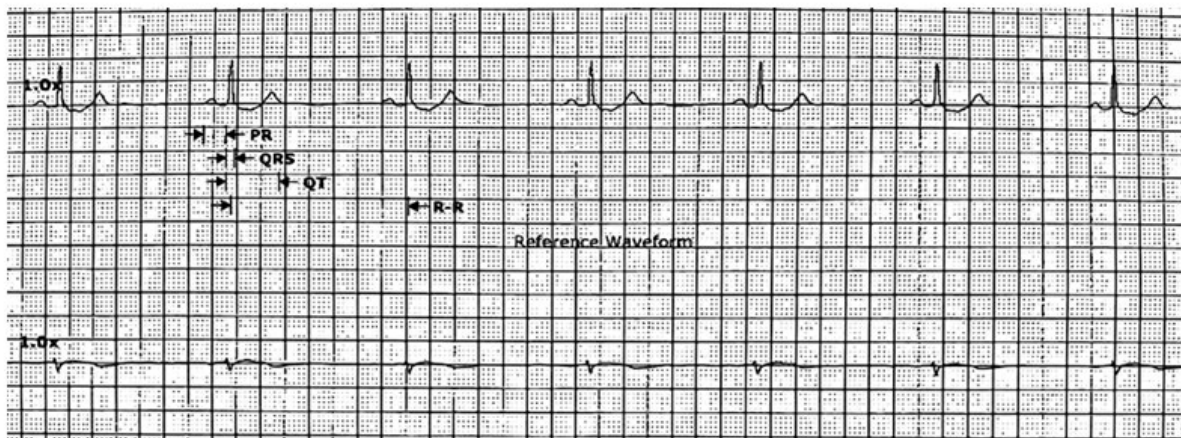


Figure 2. Telemetry strip. This is an example of what was seen on telemetry monitoring upon hospital admission. It depicts sinus bradycardia at a rate of 41 bpm (bottom).

At the emergency department, the patient was bradycardic in the mid- to low 40s bpm on telemetry. As shown in Figure 1, ECG revealed sinus bradycardia at 44 bpm with occasional PVCs and no acute ischemic changes. His initial blood work was unremarkable. Given the patient's symp-

tom, he was admitted for observation with the understanding that a pacemaker may be needed if his bradycardia worsens. His amlodipine was initially continued at a reduced dose of 5 mg daily. He was closely monitored on telemetry and found to be in persistent sinus bradycardia as low

as 41 bpm with occasional trigeminy, but no pauses were seen. A copy of his telemetry strip is provided in Figure 2. The patient continued to complain of unchanged fatigue and weakness. Amlodipine was discontinued as a trial given his symptoms. Transthoracic echocardiogram revealed normal cardiac function without significant valvular abnormalities. Treadmill stress echocardiogram found no evidence of myocardial ischemia. During the stress test, his heart rate rose from a resting rate of 58 bpm to a maximum of 135 bpm, demonstrating chronotropic competence which can be seen in Figure 3. Orthostatic vital signs were taken and were consistent with orthostatic hypotension. The case was discussed

with the cardiologist who felt that the patient was unlikely to have had an ischemic event or develop life-threatening bradyarrhythmia. Approximately 24 hrs after discontinuing amlodipine, his resting heart rate increased to low 60s bpm as depicted in Figure 4. The patient also reported improvement in his presenting symptoms of fatigue and weakness. At discharge, the patient’s heart rate was 72 bpm and blood pressure was 119/76 mmHg. He was discharged home with recommendations to avoid amlodipine for blood pressure control as it was felt to be the cause of his symptomatic bradycardia.

Stress Test

Protocol: Bruce
Total Time: 9 min : 0 sec **Total METS:** 10.50
Max ST Seg Deviation: -2.1 mm **Angina Score:** None **Duke Score:** -1
Resting HR: 83 bpm **Rest Sys BP:** 104 mmHg **Rest Dias BP:** 73 mmHg **Max Pred HR:** 149 bpm **Target HR:** 127 bpm
Peak HR: 137 bpm **Peak Sys BP:** 180 mmHg **Peak Dias BP:** 72 mmHg **% Max Pred HR:** 92 % **Max RPP:** 24,660 bpm*mmHg

Termination Reason: PROTOCOL COMPLETE, TARGET HR ACHIEVED

Stage	Duration (min)	Speed (mph)	Grade (%)	HR (bpm)	SBP (mmHg)	DBP (mmHg)	SPO2 (%)	METS	Symptoms	Comments
REST	0 min : 47 sec	0.0	0	58	128	72		---		
REST	4 min : 27 sec	0.0	0	65	107	73		---		
REST	5 min : 43 sec	0.0	0	78	104	73		---		
REST	6 min : 4 sec	0.0	0	83	104	73		---		
STAGE 1	0 min : 53 sec	1.7	10	86	104	73		---		
STAGE 1	1 min : 0 sec	1.7	10	86	104	73		---		
STAGE 1	2 min : 0 sec	1.7	10	96	104	73		---		
STAGE 1	2 min : 10 sec	1.7	10	106	104	73		---		
STAGE 1	3 min : 0 sec	1.7	10	105	144	69		---		
STAGE 2	0 min : 48 sec	2.5	12	110	144	69		---		
STAGE 2	1 min : 0 sec	2.5	12	112	144	69		---		
STAGE 2	2 min : 0 sec	2.5	12	119	144	69		---		
STAGE 2	2 min : 27 sec	2.5	12	120	178	70		---		
STAGE 2	3 min : 0 sec	2.5	12	118	178	70		---		
STAGE 3	0 min : 42 sec	3.4	14	120	178	70		---		
STAGE 3	1 min : 0 sec	3.4	14	123	178	70		---		
STAGE 3	2 min : 0 sec	3.4	14	132	178	70		---		
STAGE 3	2 min : 34 sec	3.4	14	135	180	72		---		
STAGE 3	3 min : 0 sec	3.4	14	134	180	72		---		
RECOVERY	0 min : 59 sec	0.0	0	127	180	72		---		
RECOVERY	1 min : 36 sec	0.0	0	110	180	72		---		
RECOVERY	1 min : 59 sec	0.0	0	108	143	76		---		
RECOVERY	2 min : 59 sec	0.0	0	105	137	78		---		
RECOVERY	3 min : 59 sec	0.0	0	100	137	78		---		
RECOVERY	4 min : 59 sec	0.0	0	93	131	81		---		
RECOVERY	5 min : 34 sec	0.0	0	97	131	81		---		

Figure 3. Treadmill stress test results. The patient had a resting heart rate of 58 bpm that increased to a maximum of 135 bpm towards the end of Stage 3 of the Bruce Protocol.

3. DISCUSSION

L-type voltage-gated Ca²⁺ channels, specifically the α1C subunit, are the primary target for all CCBs. The α1C subunit is subdivided into α1C-a which is found in myocardium and α1C-b which is found in smooth muscle. Additionally, DHP CCBs have higher affinity to lower resting membrane potentials, which is characteristic of smooth muscle.^[5,6] This con-

fers vasoselectivity on DHP CCBs. Due to this, DHP CCBs such as amlodipine traditionally have little chronotropic effect as they are believed to have insignificant activity in the sinoatrial and atrioventricular nodes at doses typically prescribed in clinical practice (5-10 mg).^[1,6-9] However, a study done by eHealthMe looking at post-marketing FDA data on the side effects of amlodipine found that of 33,018

people taking amlodipine, 295 (0.89%) reported bradycardia. These patients were more likely to be male, older than age 60, have been taking the medication for < 1 month, also take aspirin, and have depression.^[3] Of these 5 demographics, three of them match those of our patient. He developed symptomatic bradycardia at a dose as low as 5 mg daily, which is well within typical dosing range. We hypothesize that this could have been the result of genetic differences in the $\alpha 1C$ subunits of L-type voltage-gated Ca^{2+} channels and/or age-related impairment of hepatic clearance. Genetic differences in the $\alpha 1C$ subunits of our patient's L-type voltage-gated Ca^{2+} channels could have conferred on him a greater sensitivity to amlodipine in his cardiac tissue. As discussed above, $\alpha 1C$ subunits are the primary binding targets of CCBs and

DHP CCBs act preferentially in vascular smooth muscle due to its lower resting membrane potential. The $\alpha 1C$ -a (cardiac) and $\alpha 1C$ -b (smooth muscle) subunits are splice products from the class-C Ca^{2+} channel $\alpha 1$ gene.^[5] Studies have found that small differences in the sequence of these subunits can make them more sensitive to CCBs, allowing them to have an effect even at very low doses, as well as give CCBs greater binding affinity.^[10,11] It is possible that our patient had genetic differences in his $\alpha 1C$ -a subunits that allowed amlodipine to act despite a higher resting membrane potential and result in loss of vasoselectivity even at low doses. This hypersensitivity of $\alpha 1C$ -a subunits may also explain the bradycardia experienced by other patients.

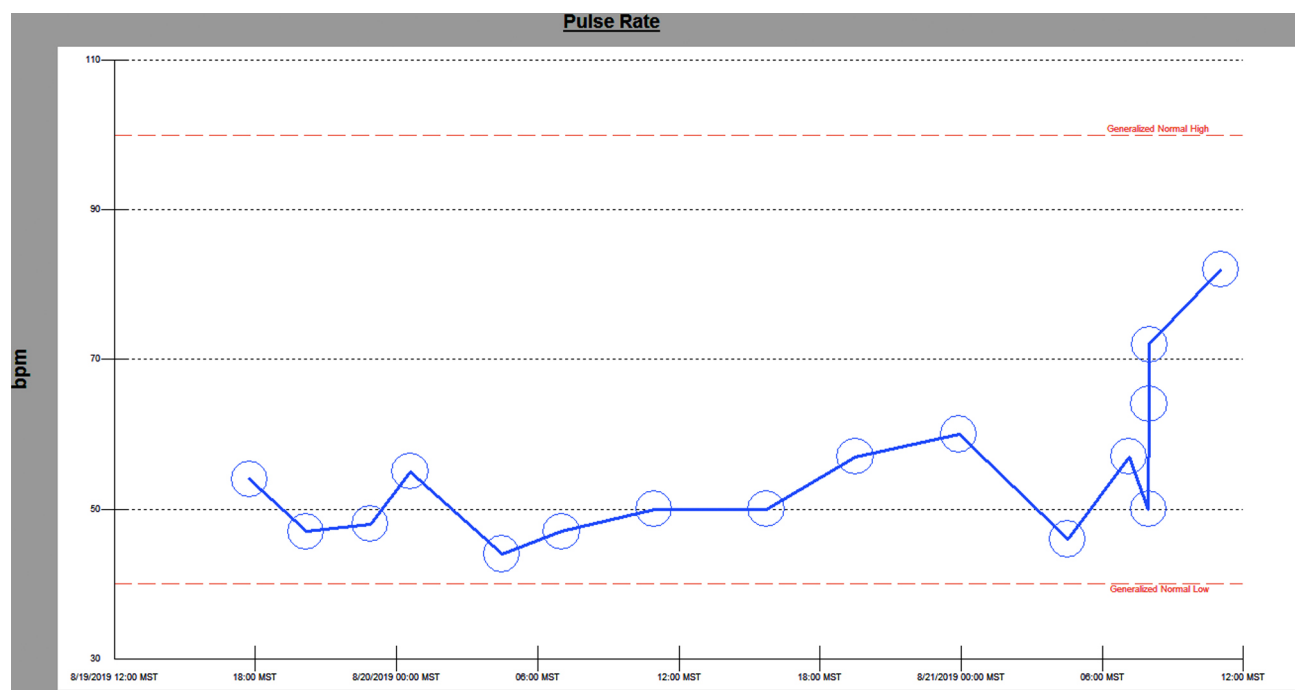


Figure 4. Pulse rate graph. This graph depicts the dramatic rise in heart rate from the mid-40s bpm to about 80 bpm after discontinuing amlodipine for 24 hours.

Another factor that may have played a role is age-related impairment of hepatic clearance. CCBs are primarily metabolized by the liver. Impaired hepatic function could lead to drug toxicity and potentially result in symptomatic bradycardia. Prior studies have found that overdose of DHP CCBs may result in loss of vasoselectivity and cause bradycardia.^[12] Two cases of fatal ingestion of 10 mg nifedipine in a 2 year old child and a 14-month old child (a toxic dose based on their body weight) resulted in severe bradycardia, refractory shock, and ultimately death. In both cases, the serum concentration of nifedipine was several fold greater than the upper therapeutic limit.^[13] Although our patient

received a typical dose of amlodipine, 5-10 mg may have proven toxic given his advanced age and probable age-related hepatic dysfunction. The Prescriber's Digital Reference for amlodipine reported that the area under the curve (AUC) may increase 40%-60% in geriatric patients due to impaired hepatic clearance with age. A reduced initiation dose of 2.5 mg daily was recommended instead. Our patient was initiated on a 5 mg dose then titrated up to 10 mg, which is higher than the recommended geriatric dose. Unfortunately, a serum amlodipine level was not measured so it is unknown if he had accumulated a toxic level on this dose.

Our diagnosis of amlodipine-induced bradycardia is a pre-

sumptive one. The resolution of his symptomatic bradycardia directly coincided with the discontinuation of amlodipine. Other possible etiologies of bradycardia were ruled out to the best of our abilities. Serum calcium was within normal limits at 9.1 mg/dl so hypocalcemia was not contributory. TSH was not elevated at 0.389 μ IU/ml so hypothyroidism was not a factor. Acute MI and structural cardiac abnormalities were ruled out based on his negative stress test and echocardiogram. Continuous cardiac monitoring on telemetry found no evidence of sick sinus syndrome or other bradyarrhythmias. Our diagnosis could have been strengthened by resuming amlodipine to document recurrence of symptomatic bradycardia. However, it would have been unethical to do so given the patient's discomfort and refusal to prolong hospitalization. It would also have been helpful to measure serum amlodipine levels to assess for toxicity. Future studies could implement these steps to show causality. Despite these limitations, our findings are consistent with recent literature

suggesting that amlodipine can cause clinically significant symptomatic bradycardia. Although the incidence is very low, identifying amlodipine-induced bradycardia is important as it resolves simply by discontinuing the drug. Failure to recognize amlodipine-induced bradycardia may result in unnecessary testing, prolonged hospital stays, and unneeded invasive procedures such as pacemaker placements or cardiac catheterization.

4. CONCLUSION

Amlodipine has the potential to cause symptomatic bradycardia despite popular belief. Genetic differences in L-type voltage-gated Ca^{2+} channels may result in hypersensitivity to the drug and lead to a relative drug toxicity. Early recognition of this infrequent side effect can help reduce unnecessary healthcare costs and improve patient outcomes.

CONFLICTS OF INTEREST DISCLOSURE

The authors have declared no conflicts of interest.

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