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DOI:
10.1093/ehjcr/ytae161

Document Version
Publisher's PDF, also known as Version of record

Citation for published version (Harvard):
Skaria, M, Hoey, E, Watkin, R & Skaria, B 2024, 'Drug-induced myocarditis precipitated by amlodipine overdose: a case report', *European heart journal. Case reports*, vol. 8, no. 4, ytae161. https://doi.org/10.1093/ehjcr/ytae161

ESC European Society of Cardiology

European Heart Journal - Case Reports (2024) **8**, ytae161
https://doi.org/10.1093/ehjcr/ytae161

CASE REPORT
Cardiovascular imaging

Drug-induced myocarditis precipitated by amlodipine overdose: a case report

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Received 24 July 2023; revised 17 January 2024; accepted 25 March 2024; online publish-ahead-of-print 27 March 2024

Background Amlodipine is the most commonly prescribed calcium channel blocker (CCB), used in the treatment of a variety of cardiovascular conditions. Calcium channel blockers remain a well-established cause of cardiovascular drug overdose. We present the case of an intentional overdose with 250 mg of amlodipine resulting in acute left ventricular dysfunction and myocarditis.

Case summary A 46-year-old man with no significant past medical history presented to the emergency department 8 h after intentionally ingesting 250 mg of amlodipine. Although initially asymptomatic with unremarkable physical examination, the patient developed progressively worsening dyspnoea over the next 2 days. Subsequent findings from chest X-ray, electrocardiogram, echocardiogram, and cardiac magnetic resonance imaging (MRI) were consistent with a diffuse myocarditis process with severe left ventricular systolic dysfunction. The patient was managed with diuretics and discharged once stable.

Discussion Our case highlights myocarditis as a potential complication of CCB overdose. Amlodipine is the most commonly prescribed CCB and is associated with cardiac toxicity at high doses. The long duration of action and high volume of distribution of amlodipine further increase the risk of morbidity and mortality from overdose. Known cardiac complications of amlodipine overdose include bradycardia, myocardial depression, and pulmonary oedema secondary to heart failure; however, diffuse myocarditis is a complication that has not previously been described in the literature. The mechanism of development of this complication remains unclear.

Keywords Myocarditis • Amlodipine • Calcium channel blocker • Cardiovascular pharmacology • Amlodipine overdose • Case report • Toxic myocarditis

ESC curriculum 2.1 Imaging modalities • 2.3 Cardiac magnetic resonance

Learning points

- Amlodipine toxicity is associated with bradycardia, myocardial depression, sinoatrial blockade, and acute heart failure.
- Amlodipine has a long half-life; symptoms of amlodipine overdose may take days to develop so patients should be closely monitored over a longer period of time.
- Awareness that amlodipine overdose may precipitate toxic myocarditis.

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Handling Editor: Giulia Ferrannini
Peer-reviewers: Bruno Rocha; Matteo Nicoletto; Federica Guidetti
Compliance Editor: Polyvios Demetriades

Summary figure

Day of overdose	Ingestion of 50 × 5 mg tablets of amlodipine.
8 h after ingestion	Patient presented to the emergency department with mild abdominal pain, otherwise asymptomatic.
12 h after ingestion	Patient was admitted to the medical ward for observation and review by the psychiatry liaison team.
36 h after ingestion	Patient was deemed medically fit and discharged from the hospital.
4 days after ingestion	Patient was brought in by ambulance with acute dyspnoea and admitted to the medical ward. He was found to have elevated troponin-T levels (>110 000 ng/dL) and pulmonary oedema.
6 days after ingestion	A cardiac MRI was performed, which showed evidence of diffuse myocarditis.
11 days after ingestion	Patient was discharged after being deemed medically fit. Echocardiogram on discharge showed a left ventricular ejection fraction (LVEF) of 45–50%.
3 months after ingestion	Cardiac MRI was repeated during outpatient cardiology evaluation, which revealed a significant improvement in myocardial inflammation.

Introduction

Amlodipine is the most commonly prescribed calcium channel blocker (CCB), used in the treatment of a variety of cardiovascular conditions. Calcium channel blockers remain a well-established cause of cardiovascular drug overdose. We present the case of an intentional overdose with 250 mg of amlodipine resulting in acute left ventricular dysfunction and myocarditis.

Case presentation

A 46-year-old man with no previous history of cardiac or psychiatric illness presented to the emergency department approximately 8 hours after intentionally ingesting 250 mg of amlodipine with alcohol. On admission, the patient was conscious with a stable blood pressure of 121/68 mmHg. Physical examination was unremarkable and electrocardiogram (ECG) on admission was normal (*Figure 1*). The patient was managed with supportive care and was discharged the next day following a psychiatric review. Two days after discharge, the patient was brought in by ambulance for progressively worsening dyspnoea. Chest X-ray showed evidence of pulmonary oedema. Troponin-T levels were >110 000 ng/L (normal <14 ng/L). Other laboratory values were normal (*Supplementary Material*). An ECG was performed, which revealed diffuse ST segment changes. A transthoracic echocardiogram was then performed, which showed severe impairment of the left ventricular systolic function and an estimated LVEF of 35–40% (normal >55%) as well as moderate mitral regurgitation. After 2 days, cardiac magnetic resonance imaging (MRI) was performed (*Figure 2*), revealing a severely impaired LVEF of 31% (end-diastolic volume 177 mL and stroke volume 56 mL) and global hypokinesia, which was particularly marked in the mid and apical segments. There was extensive circumferential gadolinium enhancement in the mid-wall,

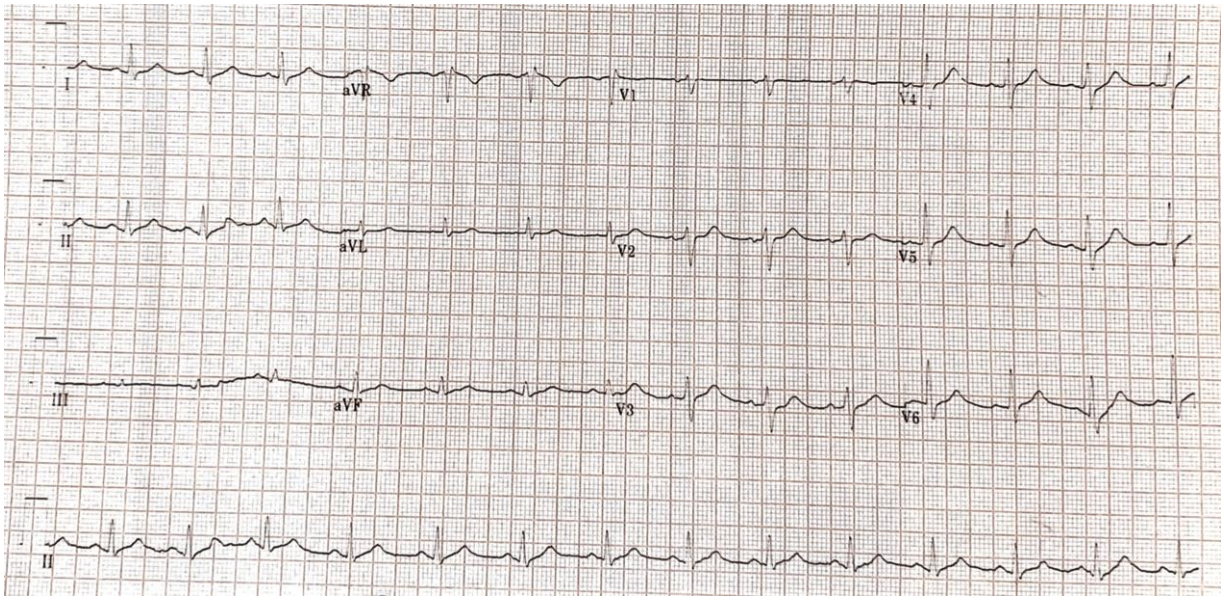

Figure 1 Twelve-lead electrocardiogram performed on patient's initial presentation. Pertinent findings include normal sinus rhythm, prolongation of the QTc (486 ms), and no significant ST segment changes.

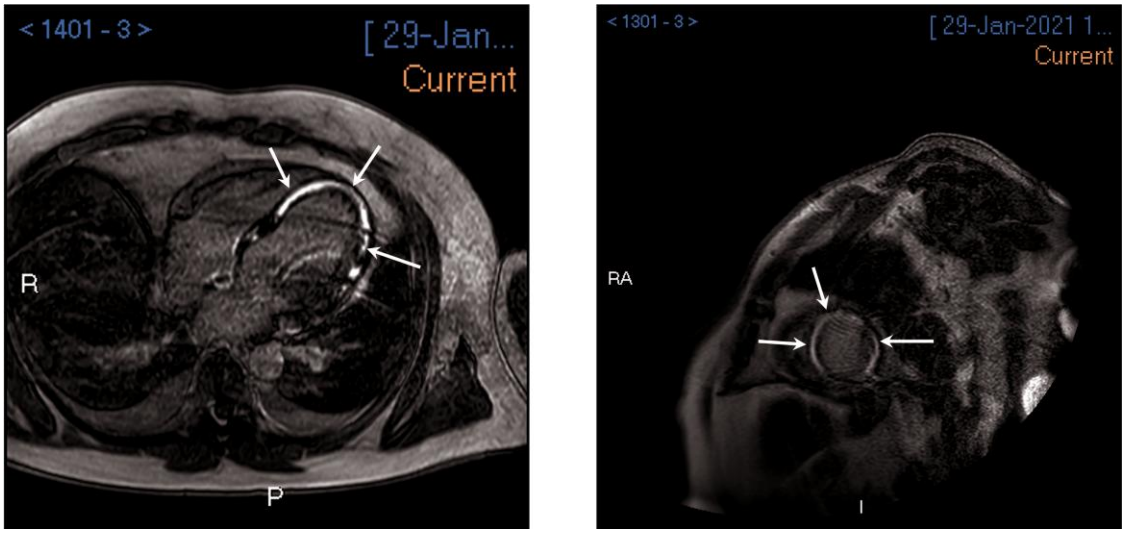

Figure 2 Four-chamber and short-axis T1-weighted inversion recovery images acquired 10 min following the administration of gadolinium-based contrast agent, showing intense global mid-wall myocardial enhancement that is not limited to a coronary artery territory and in keeping with widespread myocarditis-related change.

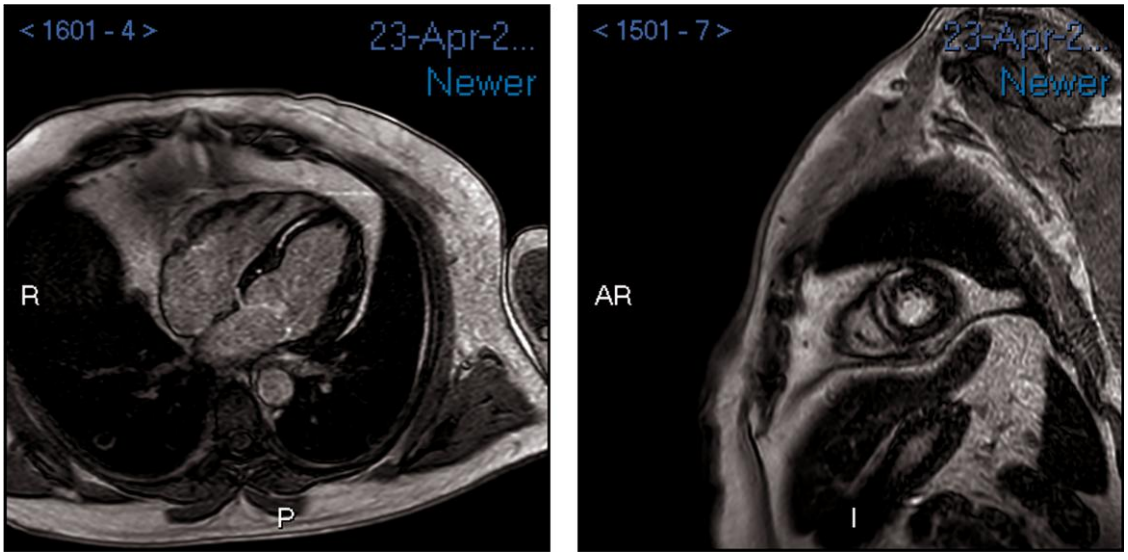

Figure 3 Repeat magnetic resonance imaging (MRI) 3 months later. Four-chamber and short-axis T1-weighted inversion recovery images acquired 10 min following the administration of gadolinium-based contrast agent showing significant interval improvement of the mid-wall myocardial enhancement.

not defined to a coronary territory and sparing the sub-endocardium. There was no evidence of left ventricular dilatation on cardiac MRI or echocardiography. These findings were consistent with a diffuse myocarditis process. The patient was managed with intravenous furosemide and discharged from the hospital once stable. On discharge, transthoracic echocardiography was repeated, showing improvement of the left ventricular function with a moderately impaired LVEF of 45–50%. The patient returned for a follow-up cardiac MRI 3 months after discharge, which showed a significant improvement in myocardial inflammation (*Figure 3*).

Discussion

Of all fatalities associated with the use of cardiovascular drugs, CCB toxicity accounts for 54% of deaths.[1] Of the CCBs licensed for prescribing in the UK, amlodipine is the most commonly prescribed and is recommended in the management of hypertension and angina pectoris according to European Society of Cardiology (ESC) guidelines.[2]

Amlodipine is a long-acting dihydropyridine CCB that predominantly affects the calcium channels in vascular smooth muscle, unlike its non-dihydropyridine counterparts that primarily affect the cardiac pacemaker cells.[3] Therefore, at therapeutic doses, amlodipine selectively acts on vascular smooth muscle. This pharmacological selectivity is lost during profound overdose, and cardiac toxicity is therefore an established complication of dihydropyridine CCB overdose.[4,5] The therapeutic dosage of amlodipine in adults is 5–10 mg once daily, with a maximum tolerated dose of 10 mg/24 h.[6]

Acute amlodipine overdose can result in binding to the alpha-1 subunit of the L-type calcium channels found in the cardiac myocytes and smooth muscle cells. This in turn prevents calcium influx and causes receptor insensitivity and cardiotoxicity.[7] Amlodipine peaks in the plasma at 6–9 h, with a half-life of 30–50 h.[6] This long duration of action, combined with a large volume of distribution (21 L/kg), increases the risk of morbidity and mortality from overdose.[7] In this case, the patient experienced a worsening of his symptoms around 48 h after ingestion. Therefore, a longer observation period in patients with amlodipine toxicity could be beneficial when assessing cardiac or systemic manifestations.

Amlodipine overdose has been associated in the literature with systemic vascular manifestations, including hypotension, coronary vasodilation, and decreased afterload.[7,8] As a result, inotropic support is often required.[8] Known cardiac manifestations of amlodipine overdose include profound bradycardia, myocardial depression, and sinoatrial nodal blockade. Pulmonary oedema secondary to heart failure is also a known complication of CCB poisoning.[5] However, in this case, we describe diffuse myocarditis as a complication of amlodipine overdose, which has not previously been described in the literature.

Toxic drug-induced myocarditis is defined as an inflammation of the myocardium resulting from illicit or medical drug use.[9] The onset of toxic myocarditis may be acute or insidious, and end-stage disease can be characterized by dilated cardiomyopathy.[9] Toxic myocarditis is frequently associated with phenothiazines, cocaine, and tricyclic antidepressant use, among others.[9] However, overuse of CCBs has not yet been associated with the development of toxic myocarditis. In our case, the patient did not take any other drugs with amlodipine, aside from an unknown quantity of alcohol. Since alcohol has been reported to occasionally cause myocardial injury,[10] it is not possible to rule out a synergistic relationship between alcohol and amlodipine in the development of myocarditis in this case. Mechanisms underpinning the development of toxic myocarditis include direct drug-induced toxicity and indirect toxicity mediated by neurohormonal responses.[11] However, there is insufficient evidence to determine whether amlodipine overdose can precipitate myocarditis by either of these mechanisms. In this case, the symptoms and signs of myocardial inflammation developed after ingestion of 25 times the therapeutic limit of amlodipine,[6] and the timing of the development of symptoms is consistent with the prolonged half-life of amlodipine.

Overall, this case report has highlighted myocarditis as a novel complication of amlodipine overdose, which has not previously been described in the literature. The pathophysiological mechanism of this complication remains unknown, so further research into this field may be needed to elucidate these mechanisms further. Currently, there is no established antidote for amlodipine overdose or specific treatment for overdose beyond supportive measures.[8,12] A greater understanding of the pathogenesis of myocarditis in this case could help to uncover more targeted treatments for cardiac manifestations of amlodipine overdose. Furthermore, this case highlights an important potential complication of CCB overdose for physician awareness.

Lead author biography

Maria Skaria is a final-year medical student at the University of Birmingham, UK.

Supplementary material

Supplementary material is available at *European Heart Journal – Case Reports* online.

Consent: The authors confirm that written consent for submission and publication of this case report, including imaging and associated text, has been obtained from the patient's family in line with COPE guidance.

Conflict of interest: None declared.

Funding: No funding source was used in this work.

Data availability

The data underlying this article are available in the article and in its online supplementary material.

References

1. Gummin DD, Mowry JB, Beuhler MC, Spyker DA, Rivers LJ, Feldman R, et al. 2021 annual report of the National Poison Data System © (NPDS) from America's Poison Centers: 39th annual report. *Clin Toxicol* 2022;**60**:1381–1643.
2. Špinar J, Vítovec J, Špinarová L, Bendová M. Combination treatment of hypertension in 2015. *Vnitr Lek* 2015;**61**:458–465.
3. Elliott WJ, Ram CVS. Calcium channel blockers. *J Clin Hypertens (Greenwich)* 2011;**13**:687–689.
4. DeWitt CR, Waksman JC. Pharmacology, pathophysiology and management of calcium channel blocker and beta-blocker toxicity. *Toxicol Rev* 2004;**23**:223–238.
5. St-Onge M, Dubé PA, Gosselin S, Guimont C, Godwin J, Archambault PM, et al. Treatment for calcium channel blocker poisoning: a systematic review. *Clin Toxicol (Phila)* 2014;**52**:926–944.
6. Meredith PA, Elliott HL. Clinical pharmacokinetics of amlodipine. *Clin Pharmacokinet* 1992;**22**:22–31.
7. Gupta B, Kerai S. Amlodipine toxicity complicated by concurrent medications. *Korean J Anesthesiol* 2018;**71**:489–490.
8. Upreti V, Ratheesh VR, Dhull P, Handa A. Shock due to amlodipine overdose. *Indian J Crit Care Med* 2013;**17**:375–377.
9. Ansari A, Maron BJ, Berntson DG. Drug-induced toxic myocarditis. *Tex Heart Inst J* 2003;**30**:76–79.
10. Zagrosek A, Messroghli D, Schulz O, Dietz R, Schulz-Menger J. Effect of binge drinking on the heart as assessed by cardiac magnetic resonance imaging. *JAMA* 2010;**304**:1328–1330.
11. Hantson P. Mechanisms of toxic cardiomyopathy. *Clin Toxicol (Phila)* 2019;**57**:1–9.
12. Ghosh S, Sircar M. Calcium channel blocker overdose: experience with amlodipine. *Indian J Crit Care Med* 2008;**12**:190–193.