

CASE REPORT

Non-Fatal Amlodipine and Insulin Overdose in an Elderly

NGO SY ADELINE¹

¹Ng Teng Fong General Hospital, National University Health System, Singapore

Abstract

Background: Amlodipine belongs to the dihydropyridine class of calcium channel blockers (CCB). We present a patient who concomitantly overdosed on amlodipine and subcutaneous insulin.

Case Presentation: An elderly man presented within 2 hours to the Emergency department after ingesting 140mg of amlodipine and self-injected 2 cartridges of NovoMix 30/70(600 units) in a suicidal attempt. He developed mild hypotension and had multiple episodes of hypoglycemia but was otherwise asymptomatic. He was managed with activated charcoal, low dose noradrenaline and multiple doses of dextrose for his hypoglycaemia. He was discharged well after 3 days.

Discussion: The clinical manifestations of dihydropyridine toxicity are hypotension, hyperglycaemia and metabolic acidosis. Our patient was elderly with multiple medical problems but he was alert and haemodynamically stable on presentation. Activated charcoal is the recommended form of decontamination when the patient presents early. He also developed initial hyperglycemia, which correlates with the degree of the calcium channel blocker overdose. The early coadministration of insulin would correct the patient's hyperglycemia, acidosis, myocardial function and even provide inotropic support. It may be possible that the subcutaneous route of administering high dose insulin has similar effects as those of intravenous HIET.

Our patient's hypoglycaemia occurred about 12 hours of the overdose, which is expected after an insulin overdose. He required many boluses of dextrose infusions before his blood sugar level stabilised.

Conclusion: It is postulated that self-administration of insulin and early decontamination could have resulted in patient's good outcome despite having ingested a potentially fatal dose of amlodipine.

Keywords: Amlodipine; Hypotension; Insulin; Overdose

How to cite this article: Adeline NS. Non-Fatal Amlodipine and Insulin Overdose in an Elderly. *Asia Pac J Med Toxicol* 2018;7:20-3.

INTRODUCTION

Amlodipine belongs to the dihydropyridine class of calcium channel blockers (CCB). It is used in the treatment of hypertension, angina and for angina prophylaxis. Fatal doses of amlodipine have been reported at doses as low as 50mg to being toxic at doses as low as 30 mg (1, 2). It is unusual that elderly patients with multiple medical problems with ingestion of up to 140mg of amlodipine present with only minimal symptoms.

We present a patient with a significant overdose of amlodipine who concomitantly overdosed himself with subcutaneous insulin. He presented only with transient mild hypotension and was subsequently discharged well. We believe this to be the first case of concomitant amlodipine and subcutaneous insulin overdose reported in literature. Causes of his relatively uncomplicated clinical course are discussed.

CASE PRESENTATION

A 75-year-old man with a past medical history of diabetes mellitus with retinopathy and nephropathy, hypertension, hyperlipidaemia, chronic eczema and lacunar stroke presented to the emergency department 2 hours after he was

witnessed by his caregiver to have ingested 28 tablets of amlodipine 5 mg each (total 140 mg). He had also intentionally injected himself with 2 cartridges of insulin NovoMix 30/70 (3 mL each of 100 unit/mL, soluble insulin aspart/protamine-crystallised insulin aspart in the ratio 30/70, equivalent to 3.5 mg, total up to 600 unit). The patient was depressed and took the overdose with suicidal ideation. Although his caregiver had witnessed the ingestion, she delayed calling for the ambulance after first trying to contact the patient's family members for advice. She had witnessed the patient taking his usual medications four hours before and became suspicious after seeing the patient take his medications again, prompting her to confront the patient. He was forthcoming with the history, appeared despondent but was otherwise asymptomatic. His usual medications included 5mg amlodipine, 25mg of atenolol, linagliptin 5mg, atorvosatin 40 mg and novoMix 30/70 (36U after breakfast and 16U after dinner) daily. He had taken his usual medications as prescribed on the same day of the overdose.

His initial blood pressure was 141/76 mmHg, pulse was 94 per minute and regular, respiratory rate was 18 per minute and he was maintaining a saturation of 100% on room air. His cardiac and neurological examination was essentially normal.

*Correspondence to: Ngo SY Adeline; MD. Ng Teng Fong General Hospital, National University Health System, Singapore
1 Jurong East Street 21 Singapore 609606
Tel: +65 6716 2000, Fax: +65 6716 5500, E-mail: angosy@gmail.com
Received 04 February 2018; Accepted 03 March 2018

His electrocardiogram (ECG) showed a normal sinus rhythm. Bedside blood sugar level was 432 mg/dl. The initial venous blood gas, cardiac enzymes and full blood count levels were within normal limits. His renal panel was within his baseline levels. Plain chest radiography was normal. Corrected calcium level was 2.29 mmol/L (2.2 to 2.7 mmol/L). His serum lactate level was 2.0 (0.5-2.2 mmol/L). His bedside echocardiography revealed normal cardiac systolic function.

The patient was treated with 50g of activated charcoal and intravenous slow bolus of calcium gluconate 20mg. His bedside blood sugar level was monitored at 2 hourly intervals. After 8 hours, the patient's blood pressure dropped to 95/78mmHg and his pulse rate was 80 per minute. He was initially supported with a low dose of intravenous noradrenaline which was weaned off after a few hours. He was monitored in the high dependency unit in anticipation of a worsening haemodynamic course. The patient's blood pressure ranged between (107-150)/(61-92)mmHg with a mean arterial pressure above 60mmHg throughout the period of observation. He had multiple episodes of hypoglycaemia which required boluses of Dextrose 50% and Dextrose 10% solution.

After almost 24 hours post overdose, the patient's haemodynamics and blood sugar level remained stable. He had no complaints related to the amlodipine overdose during his hospitalisation. He was discharged home after a psychiatric evaluation for his depression and a hospital stay of 3 days. His blood pressure was 138/68 mmHg and his blood sugar level was 252 mg/dl prior to discharge.

DISCUSSION

Our case shows that a potentially fatal dose of 140 mg amlodipine may result in minimal symptoms with a good outcome, possibly due to the co-administration of a large dose of insulin at the same time as the CCB overdose, which could have prevented its complications. This is contrary to the patient's intent for a successful suicide.

Amlodipine overdose often results in extended effects due to its prolonged half-life of between 30–50 hours (3). The clinical manifestations of CCB toxicity are mainly due to the hindered movement of calcium into the cell membrane. Hence peripheral vasodilation and myocardial depression occur as a result of this inhibition of voltage-sensitive L-type calcium channels (4).

Although amlodipine has a higher selectivity for vascular smooth muscle than for the myocardium, this selectivity can be lost in overdoses. Amlodipine is slowly absorbed after oral ingestion, and peak plasma concentrations occur between 6 to 9 hours after ingestion. Patients may present with hypotension, bradycardias, conduction blocks, pulmonary oedema, hyperglycaemia and metabolic acidosis (5). As many CCBs may be formulated as modified-release products, the onset of their symptoms may be delayed (6). Thus, our patient was monitored for an extended period in the high dependency area where constant monitoring in anticipation of hypotension and where immediate intervention was possible.

The recommended maximum therapeutic dose of amlodipine is 10mg daily and life-threatening effects have

been reported at just slightly greater doses than those used for therapy (7). Our patient presented relatively well and had normal haemodynamics at presentation even though he was elderly with multiple medical problems, including nephropathy. One would have expected a poor outcome for him. It is uncommon to have patients with amlodipine overdose present with only mild symptoms of toxicity or survived after minimal supportive management (8, 9).

As our patient presented alert and haemodynamically stable to the Emergency department about 2 hours after his overdose, he was treated with activated charcoal. This is recommended as a form of decontamination even if patients present after one hour post poisoning if there is a potential benefit (7). Activated charcoal almost completely prevented amlodipine absorption when it was administered instantly after amlodipine ingestion. It also reduced amlodipine absorption when its administration was delayed by 2 hours or more, with no significant negative effects being reported with its use (10). Whole bowel irrigation could also be considered as a form of decontamination although this is usually recommended for overdose of sustained-release products or in massive overdoses (7).

CCB also blocks the L-type calcium channels in the pancreatic islets cells. This gives rise to hyperglycemia and acidosis due to diminished insulin release and enhanced insulin resistance (11). It has also been found that the serum glucose concentrations correlate directly with the degree of the calcium channel blocker overdose (12). It is highly probable that our patient ingested a significant overdose of amlodipine as he presented with hyperglycaemia rather than hypoglycaemia which is consistent with the prognostic value of the serum glucose concentration despite also overdosing on a substantial dose of Novomix insulin post 2 hours.

NovoMix 30/70 is an insulin analogue, possessing both a rapid-acting and an intermediate-acting effect, in the ratio 30/70 100 units/ml suspension for injection in a pre-filled pen 30% soluble insulin aspart and 70% insulin aspart crystallised with protamine (13). The onset of action of subcutaneously injected NovoMix 30 is within 20 minutes. It should be expected that by the time of our patient's presentation, the effect of Novomix would be at its maximum. He would have injected between 300 to 600 units of soluble insulin aspart/protamine-crystallised insulin aspart since he had injected himself with 1 and a half-filled penfills. The use of insulin would correct the patient's hyperglycemia, acidosis, myocardial function and even provide inotropic support (14). Our patient had injected himself with insulin at almost the same time as his amlodipine overdose ingestion. This unintentional early use of insulin could have benefitted our patient. Many reports with the early use of high-dose insulin euglycaemic therapy (HIET) in CCB overdose found the outcomes safe and efficacious, hence the early and appropriate use of high-dose insulin (intravenous (iv) bolus of 1.0 unit/kg followed by a 0.5–2.0 unit/kg/h infusion) therapy (HIET) has now been accepted as a standard treatment strategy in patients with large overdoses of CCB (15-17). Although various case reports published in literature have reported differing

treatment algorithms, experts have recently recommended dosages starting with a bolus intravenous insulin of 1.0 unit/kg followed by a 1 unit/kg/h infusion, to be titrated up to 10 unit/kg/h (18).

There have been no known prior reports on the use of high doses of insulin via subcutaneous route for the management of CCB overdose. There are very few studies that evaluate the pros and cons between the use and effects of subcutaneous versus intravenous use of insulin, and these are usually for the treatment of diabetic ketoacidosis. Based on low quality evidence, there are no known advantages or disadvantages of using one route over the other (19). One may hypothesise that the subcutaneous route of administering high dose insulin may have a place in the management CCB overdose, especially if the intravenous access in a patient is compromised. There may be a possible role in the prehospital setting where large doses of intravenous insulin infusion may be difficult to administer. However, to date, there are no known studies of such. Although high-dose insulin has been strongly recommended for patients with documented myocardial dysfunction because it provides a positive inotropic effect, its use is also recommended to improve the hemodynamic functions in patients with dihydropyridines poisoning with no evidence of myocardial dysfunction but with haemodynamic compromise (18).

Our patient's cardiac function on echocardiography did not appear to be affected by the overdose. His blood pressure was transiently low and he was supported with a low dose of noradrenaline which was easily weaned off after a few hours. Noradrenaline was the inotrope of choice as it has predominantly alpha-agonistic effect. This is consistent with poisoning from amlodipine, which has limited myocardial binding, hence poisoning usually presents with hypotension and reflex tachycardia or a normal heart rate, which was the case with our patient.

Our patient's glycaemic control became difficult to control after about 12 hours of the overdose, which is also to be expected from a large overdose of insulin. This has also been reported with HIET therapy (14). Our patient required many boluses of D50% and D10% infusions before his blood sugar level stabilised within 24 hours of the overdose. This is consistent with the maximum effect of novomix, which will occur between 1-4 hours after injection and the duration of effect which may last for up to 24 hours. However, with an overdose, the duration of action can be protracted and the peak effect may be delayed and prolonged. This is due to the accumulation, extended insulin half-life and reduced absorption from the injection site (20). This is also dependent on the dose rather than the type of insulin (21). Hence, our patient was monitored for at least another day even after the blood sugar level was seemingly normal.

CONCLUSION

This is the first known case of a mixed overdose of amlodipine with a large overdose of subcutaneous insulin. We believe that our elderly patient's good outcome with minimal haemodynamic compromise despite overdosing on

a potentially fatal dose of amlodipine and insulin was due to a combination of early decontamination with activated charcoal, as well as the concomitant overdose on a large amount of subcutaneous insulin.

REFERENCES

1. Cosby SH, Carson DJ. A fatal case of amlodipine poisoning. *J Anal Toxicol* 1997;21:221-2.
2. Hung YM, Olson KR. Acute amlodipine overdose treated by high dose intravenous calcium in a patient with severe renal insufficiency. *Clin Toxicol (Phila)* 2007; 45: 301-3.
3. DeWitt CR, Walksman JC. Pharmacology, pathophysiology and management of calcium channel blocker and β -blocker toxicity. *Toxicol Rev* 2004; 23:223-38.
4. Jang DH, DeRoos FJ. Calcium channel blockers. Goldfrank's Toxicologic Emergencies. 10th ed. New York, USA: McGraw-Hills; 2015.
5. Ferrari R. Major differences among the three classes of calcium antagonists. *Eur Heart J* 1997; 18:A56-70.
6. Ramoska EA, Spiller HA, Winter M, et al Borys D. A one-year evaluation of calcium channel blocker overdoses: toxicity and treatment. *Ann Emerg Med* 1993; 22:196 - 200.
7. Olson KR, Erdman AR, Woolf AD, Scharman EJ, Christianson G, Caravati EM et al. American Association of Poison Control Centers. Calcium channel blocker ingestion: an evidence-based consensus guideline for out-of-hospital management. *Clin Toxicol (Phila)* 2005;43:797-822.
8. Poggenborg RP, Videbæk L, Jacobsen IA. A Case of Amlodipine Overdose. *Basic Clin Pharmacol Toxicol* 2006; 99: 209-12.
9. Stanek EJ, Nelson CE, DeNofrio D. Amlodipine overdose. *Ann Pharmacother* 1997;31:853-6.
10. Laine K, Kivisto K T, Laakso I, Neuvonen PJ. Prevention of amlodipine absorption by activated charcoal: effect of delay in charcoal administration. *Br J Clin Pharmacol* 1997; 43:29-33.
11. Salhanick SD, Shannon MW. Management of calcium channel antagonist overdose. *Drug Safety* 2003; 26: 65-79.
12. Levine M, Boyer EW, Pozner CN, Geib AJ, Thomsen T, Mick N et al. Assessment of hyperglycemia after calcium channel blocker overdoses involving diltiazem or verapamil. *Crit Care Med* 2007;35:2071-5.
13. [No author]. NovoMix 30 Penfill 100 units/ml, NovoMix 30 FlexPen 100 units/ml. 2017. Available from: <http://www.medicines.org.uk/EMC/medicine/8591/SPC/NovoMix+30+Penfill+100+U+ml%2C+NovoMix+30+FlexPen+100+U+ml/> (Accessed Sep 5, 2017)
14. Engebretsen KM, Kaczmarek KM, Morgan J, Holger JS. High-dose insulin therapy in beta-blocker and calcium channel-blocker poisoning. *Clin Toxicol (Phila)* 2011; 49:277-8.
15. Shepherd G, Klein-Schwartz W. High-dose insulin therapy for calcium-channelblocker overdose. *Ann Pharmacother* 2005;39:923-30.
16. Espinoza TR, Bryant SM, Aks SE. Hyperinsulin therapy for calcium channel antagonist poisoning: a seven-year retrospective study. *Am J Ther* 2013;20:29-31.
17. Holger JS, Stellpflug SJ, Cole JB, Harris CR, Engebretsen KM. High-dose insulin: a consecutive case series in toxin-induced cardiogenic shock. *Clin Toxicol (Phila)* 2011;49:653-8.
18. St-Onge M, Anseeuw K, Cantrell FL, Gilchrist IC, Hantson P, Bailey B et al. Experts Consensus Recommendations for the Management of Calcium Channel Blocker Poisoning in Adults. *Crit Care Med* 2017; 45:e306-e315.

19. Andrade-Castellanos CA, Colunga-Lozano LE, Delgado-Figueroa N, Gonzalez-Padilla DA. Subcutaneous rapid-acting insulin analogues for diabetic ketoacidosis. *Cochrane Database Syst Rev* 2016 Jan 21;(1): CD011281.
20. Ohyama T, Saisho Y, Muraki A, Kawai T, Itoh H. Prediction of recovery time from hypoglycemia in patients with insulin overdose. *Endocr J* 2011; 58:607–11.
21. Hildebrandt P, Birch K, Sestoft L, Vølund A. Human Monotard insulin: dose-dependent subcutaneous absorption. *Diabetes Res* 1984; 1:183–5.