Case report

Amlodipine-induced hyperglycaemia

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Abstract
The risk of hyperglycaemia induced by use of amlodipine is rare and not well established. This case report provides evidence that significant and reversible changes in glycaemic control may occur with standard use of amlodipine as an antihypertensive agent. Copyright © 2018 John Wiley & Sons.

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diabetes; amlodipine; hyperglycaemia

Introduction
When initiating pharmaceutical management for a chronic disease, the possible risks of therapy are carefully balanced against the potential benefits. In the case of hypertension, side effects such as cough, imbalances in electrolytes, bradycardia, and orthostatic hypotension are common adverse events associated with the major classes of antihypertensive agents.

Most adverse events can be managed with proper monitoring. Although less common, medication-induced hyperglycaemia has been identified for some antihypertensive therapies and can be sufficiently significant to result in a diagnosis of diabetes. This particular adverse event is not always readily detected and is difficult to prevent. Hyperglycaemia occurs most often related to thiazide diuretics and beta blockers, yet amlodipine is the likely culprit responsible for the incidence of significant hyperglycaemia in the case described below.

Amlodipine, a dihydropyridine calcium channel blocker, exerts its antihypertensive effects via the blockade of calcium channels in smooth muscle in the periphery. The role of calcium in this area is to promote vasoconstriction and maintain vascular muscle tone. By blocking calcium’s ability to act, the muscles of the blood vessels relax leading to a reduction in vascular resistance and thus a decrease in blood pressure.¹ It is the ability to block calcium that is proposed to potentially lead to hyperglycaemia. The calcium blockade of amlodipine is believed to affect certain L-type calcium channels of the pancreas.²,³ These channels rely upon calcium for the release of insulin into the body and, without the regular influx of calcium, insulin is not released as it normally would be. Over time this inability to release insulin can result in significant hyperglycaemia, potentially to the point of a diagnosis of diabetes.²,³ Amlodipine has also been possibly linked to advanced glycation end-product changes that may also affect hyperglycaemia; however, the effect has yet to be determined by current research.⁴

Previous studies on the adverse effects of antihypertensive medications have noted an increased incidence of new-onset diabetes. In the ALLHAT trial, chlorthalidone was found to have a significantly higher incidence of hyperglycaemia and new-onset diabetes than either amlodipine or lisinopril, with lisinopril having the lowest incidence of the group.⁵ The VALUE study further reinforced the greater risk of developing diabetes while on amlodipine compared to angiotensin converting enzyme inhibitors and angiotensin receptor blockers.⁶ This study found that, compared tovalsartan, patients taking amlodipine had a 2.1% greater absolute risk of developing diabetes over a four-year period in spite of no statistically significant differences in patient risk factors for diabetes.⁶

A thorough search elicited no published case reports describing amlodipine-induced hyperglycaemia. Although a small and not well-established risk, the specific circumstances and timeline of the diagnosis and resolution of hyperglycaemia in the following patient case are remarkable.
Case report

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Case history
In December 2016, a 57-year-old white female was diagnosed with essential hypertension. At this time she was prescribed amlodipine 5mg daily. The patient’s other medications included a multivitamin, vitamin D3 2000IU daily, omega-3 1200mg daily, and aspirin 81mg daily. No changes were made to these medications or any additional medications utilised over the course of the case. In mid-February, the patient requested that her amlodipine be reduced to half of her dose twice daily, noting the onset of polydipsia and polyuria as well as vision changes. These changes were initially noticed approximately three weeks after beginning amlodipine therapy, prompting an optometry appointment where the optometrist recommended to seek testing for diabetes. At the patient’s next follow up with primary care on 20 February 2017, her haemoglobin A1c (HbA1c) was 9.1% (76mmol/mol) and fasting blood glucose was 305mg/dL, giving a diagnosis of diabetes, as per American Diabetes Association guidelines.\(^7\) The patient had no noted previous glycaemic issues with a prior HbA1c drawn in November 2015 of 4.9% (30mmol/mol) and a fasting blood glucose reading within normal limits in December 2016 when diagnosed with hypertension. Other pertinent laboratory values from this time were within normal limits.

Based on the concern that the hyperglycaemia may be related to amlodipine, the patient was instructed to discontinue amlodipine and was prescribed a combination therapy of lisinopril and hydrochlorothiazide to replace amlodipine. The patient, however, refused to begin this regimen and decided to have no pharmacological treatment for her hypertension. The patient was referred to a pharmacist possessing credentials as a certified diabetes educator (CDE) for pharmacological management of diabetes. The patient was provided with a blood glucose meter and advised to check her blood glucose for improved monitoring of control. At the follow-up appointment with her primary care physician a month after her formal diagnosis, she reported that her fasting blood glucose readings had rapidly decreased to below 100mg/dL from readings in the first three weeks after diagnosis and this was maintained through to her later appointment with her pharmacist. Limited lifestyle changes were made including a decrease in soda intake, increase of vegetable intake by an unspecified amount, and no change in exercise regimen. No significant change in weight or BMI was noted during all visits throughout the case.

In early March, within three weeks of her primary care appointment, the patient began seeing the pharmacist. After consultation with the patient, the recommendation was to trial lifestyle changes in lieu of pharmacological management of diabetes. The patient was provided with a blood glucose meter and advised to check her blood glucose for improved monitoring of control. At the follow-up appointment with her primary care physician a month after her formal diagnosis, she reported that her fasting blood glucose readings had rapidly decreased to below 100mg/dL from readings in the first three weeks after diagnosis and this was maintained through to her later appointment with her pharmacist. Limited lifestyle changes were made including a decrease in soda intake, increase of vegetable intake by an unspecified amount, and no change in exercise regimen. No significant change in weight or BMI was noted during all visits throughout the case.

A week later the patient reported back to the pharmacist for follow up and further reported that the majority of her blood glucose readings were below 100mg/dL. Given the improvement in blood glucose, it was recommended that the patient continue with current lifestyle interventions without the addition of pharmacological agents.

Three months after formal diabetes diagnosis, in May the patient reported back to her primary care physician for further laboratory values to be drawn. At this visit, her HbA1c was 5% and all other laboratory test results remained within normal limits. During this timeframe, the patient did not experience any infections or use other medication therapies, such as steroids typically associated with hyperglycaemia. As no medications for the treatment of diabetes were started and the patient had a significant decrease in HbA1c, the diagnosis of diabetes was removed. The patient also consented to resume antihypertensive therapy with a single agent, lisinopril.

Discussion
This case shows a drastic change in glycaemic control potentially based
on the introduction of an antihypertensive medication. Although not able to state with absolute certainty that the hyperglycaemia was caused by amlodipine in this case, there was a rapid change in glycaemic control and typical signs and symptoms of hyperglycaemia with the introduction and within two weeks of cessation of the medication, and no other identifying causes were found. The patient did make some therapeutic lifestyle changes that could have also impacted on the glycaemic control; however, based on the minimal amount of changes described above, the profound change in HbA1c is not likely to be significantly affected by this. Notably, the patient’s BMI stayed within one point throughout the duration of treatment, and was greater at the time of the resolution of the hyperglycaemia. No other medication therapies were changed over the course of treatment to affect the results. Overall, the four-point increase and sequential decrease in HbA1c are most likely related to the initiation and cessation of amlodipine. Utilising the Naranjo scoring tool, the association of amlodipine causing the hyperglycaemia was rated as a ‘possible association’.8

Previous literature, as described above, indicates the proposed mechanism of hyperglycaemia and some examples of limited occurrence; however, hyperglycaemia induced by amlodipine is not well established. Current recommendations for the medication do not include regular testing or monitoring of glucose.1 The most recent American Diabetes Association and American Association of Clinical Endocrinologists guidelines for diabetes do not provide any guidance on monitoring or use of the medication or its class when managing diabetes.7,8 Alderman et al. established previously that amlodipine and calcium channel blockers are a low risk compared to other antihypertensive medications for causing hyperglycaemia.9 Abe et al. also established that no significant change in the incidence of hyperglycaemia was seen when using amlodipine in patients with chronic kidney disease.11 Barzilay et al. found that amlodipine was metabolically neutral when compared to medications like chlorothalidone and beta blockers.2

The risk of hyperglycaemia with the use of amlodipine is potentially significant for several reasons. First, calcium channel blockers, including amlodipine, are a frequently recommended and utilised medication for hypertension, which is a common comorbidity of diabetes. Healthcare providers must be aware of the consequences of potentially increasing the risk of developing diabetes. Second, amlodipine use could also have an impact on the control of an individual’s already established diabetes. Third, as both hypertension and diabetes increase the risk of cardiovascular disease, lack of control of either disease state can result in profound implications. Many patients require multiple medications to reach established blood pressure goals and potentially eliminating a current cost-effective option could be significant. The relative lack of appreciation of this association by the general health care population speaks to the importance of this case report to improve recognition among providers so that incident hyperglycaemia may be avoided or corrected.

This case report provides evidence that significant and reversible changes in glycaemic control may occur with standard use of amlodipine as an antihypertensive agent. The association of amlodipine and hyperglycaemia warrants further study in order to better establish the impact on disease state management decisions and to determine if any risk factors can be identified.

**Declaration of interests**
There are no conflicts of interest declared.

**References**