

Probable Amlodipine-Induced Angioedema

Jessica Southward, Elizabeth Irvine, and Marina Rabinovich

Angioedema is a potentially life-threatening, abrupt swelling of the skin and/or mucous membranes that sometimes involves the upper respiratory and gastrointestinal tracts.¹⁻³ While the differential diagnosis for angioedema is quite broad, including allergic, immune-mediated, and acquired causes, the most common precipitating factor is drugs.² The most common drug class associated with angioedema is angiotensin-converting enzyme (ACE) inhibitors, with an overall incidence of 0.1–2.2%, followed by angiotensin receptor blockers (ARBs), with an estimated incidence of less than 0.1%.^{1,3-5} Additional drugs reported to cause angioedema include amiodarone, nonsteroidal antiinflammatory drugs, estrogen, famotidine, fosphenytoin, and fibrinolytic agents.^{1,6,7}

While the number of published case reports regarding calcium-channel blocker (CCB)-induced angioedema is limited, a study conducted in Sweden by Hedner et al.⁸ determined that CCBs are the second most common drug class associated with angioedema when compared with ACE inhibitors, β -adrenergic blockers, and diuretics. Angioedema was reported in 36 cases of ACE inhibitor use, 11 cases of diuretic use, 11 cases of β -blocker use, and 14 cases of CCB use. At the time this research was conducted ARBs were not on the market.

A review of the literature using EMBASE (1980–May 2008) and MEDLINE (1950–May 2008) using the search terms angioedema, calcium-channel blocker, and amlodi-

OBJECTIVE: To report a case of angioedema likely associated with amlodipine administration in a patient with a right thalamic hemorrhagic stroke.

CASE SUMMARY: A 50-year-old female experienced angioedema during hospitalization for a right thalamic hemorrhagic stroke. She had no past history of angioedema and all of her medications were assessed for risk of angioedema. After careful evaluation, case reports linking calcium channel blockers (CCBs) and angioedema led to further examination of amlodipine as a cause. Amlodipine therapy had been initiated 24 hours prior to the development of angioedema, which then resolved 72 hours after discontinuation of the drug. In total, the patient experienced oropharyngeal swelling for 10 days.

DISCUSSION: In determining a cause for the patient's angioedema we eliminated genetic, allergic, physically induced, thyroid autoimmune disease-associated, and medication-induced causes. Three case reports describing 7 patients have linked the CCBs verapamil, diltiazem, and nifedipine with angioedema. The onset and resolution of symptoms in our patient were very similar to those seen in other case reports. Application of the Naranjo probability scale found a probable link between amlodipine and angioedema.

CONCLUSIONS: Although few reports of CCB-induced angioedema exist, to our knowledge, this is the first reported case to suggest a link between angioedema and amlodipine therapy. Clinicians should consider amlodipine as a potential cause of angioedema.

KEY WORDS: amlodipine, angioedema, calcium-channel blocker.

Ann Pharmacother 2009;43:772-6.

Published Online, 18 Mar 2009, www.theannals.com, DOI 10.1345/aph.1L527

pine identified 7 case reports. The CCBs in these case reports were verapamil, diltiazem, and nifedipine.^{8,9} To date, there have been no published case reports of amlodipine-induced angioedema. We present a case of severe angioedema linked to the administration of amlodipine in a patient with a right thalamic hemorrhagic stroke.

Case Report

A 50-year-old African American female with a past history of uncontrolled hypertension, asthma, and stage 5 chronic kidney disease presented with sudden-onset left

Author information provided at the end of the text.

hemiplegia. Her social history was significant for tobacco and cocaine use for an unspecified period of time. She had no known drug allergies and admitted to being nonadherent to her home medications, which included clonidine 0.3 mg twice daily, sustained-release verapamil 240 mg daily, valsartan 160 mg daily, extended-release metoprolol 150 mg daily, ranitidine 150 mg twice daily, and cinacalcet 60 mg daily. The patient denied the use of herbal supplements, over-the-counter medications, or other supplements. There had been no recent changes in the drug regimen based on the patient's prescription record at the hospital's outpatient pharmacy. She had no history of taking any CCB other than verapamil, which had been prescribed for multiple years, although she was nonadherent.

Physical examination revealed a slight left facial droop and left upper and lower extremity weakness. Based on the patient's symptoms and elevated blood pressure of 214/125 mm Hg, a diagnosis of hypertensive emergency was made and a continuous infusion of labetalol was initiated (Figure 1). Computed tomography of the head revealed a 2.9 × 2.2 centimeter hemorrhage of the right basal ganglia. Shortly after presentation, the patient developed

cardiac arrest with pulseless electrical activity, requiring intubation and initiation of cardiopulmonary resuscitation. During the resuscitation attempt, atropine and epinephrine were administered; however, medications for intubation were not required. After resuscitation, a chemistry panel revealed potassium 7.9 mEq/L (reference range 3.4–5.1) and blood urea nitrogen 94 mg/dL (8–22), at which point emergent hemodialysis was initiated. Other pertinent laboratory test results included thyroid-stimulating hormone 4 mIU/mL (0.34–5.5) and an unremarkable complete blood cell count. The patient remained hypertensive despite hemodialysis and use of the maximum dose of labetalol via continuous infusion (6 mg/min); therefore, therapy was transitioned to a continuous infusion of nicardipine 5 mg/h on day 1 of hospital admission. Upon arrival to the neurology intensive care unit, infusions of propofol and fentanyl were initiated for sedation along with intravenous fosphenytoin 100 mg every 8 hours for seizure prophylaxis. On day 3, intravenous famotidine 20 mg every 12 hours was initiated for stress ulcer prophylaxis. On day 4, after the blood pressure had been stabilized for several days, the decision was made to slowly taper intravenous nicardipine

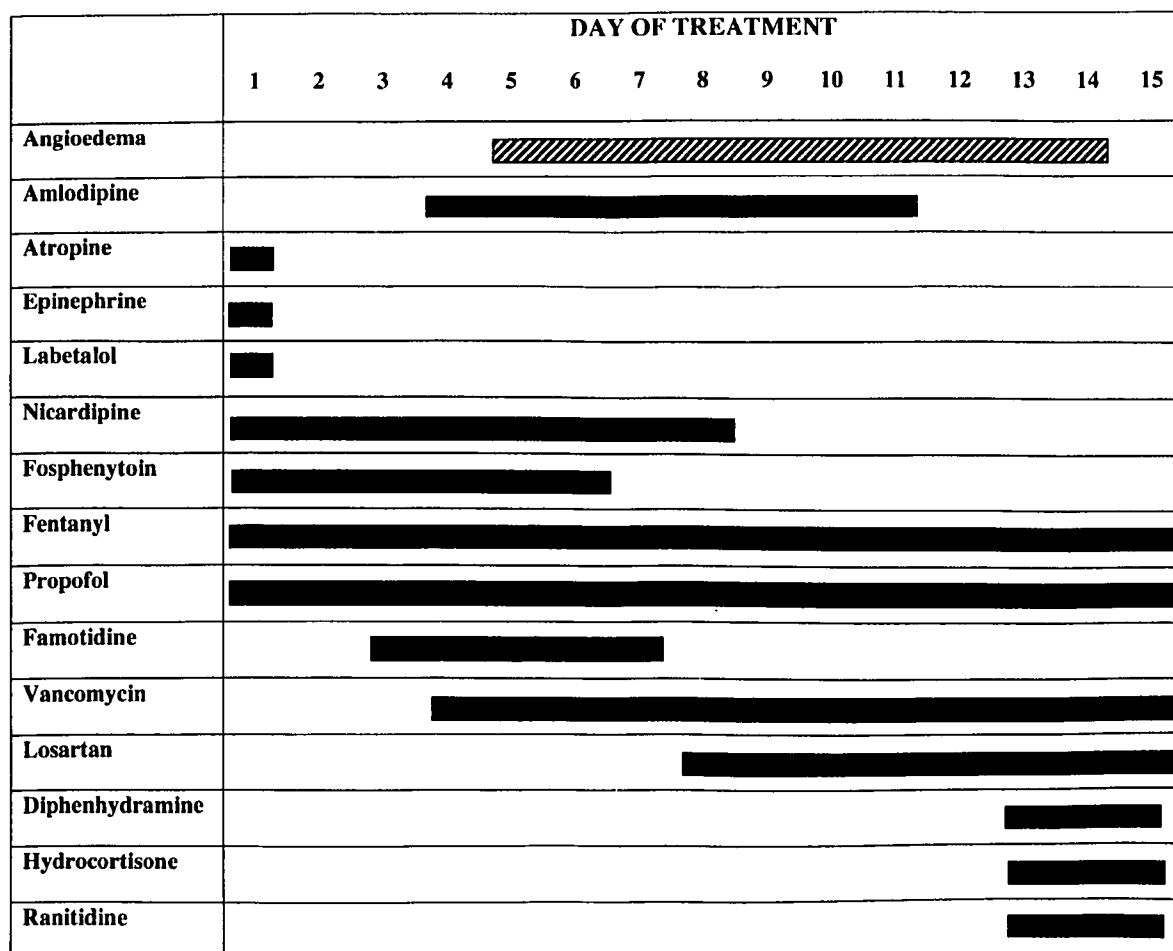


Figure 1. Medication administration timeline in relation to angioedema.

to discontinuation and initiate oral antihypertensive therapy with amlodipine 10 mg daily via nasogastric tube. On the same day, the patient became febrile and therapy with vancomycin 1 g was initiated and administered after each dialysis session on Monday, Wednesday, and Friday.

On day 5, approximately 24 hours after the initiation of amlodipine, the patient developed swelling of the face and tongue, which was consistent with signs of angioedema. Fosphenytoin and famotidine were discontinued on days 6 and 7, respectively, due to their possible risk of facial edema and angioedema.^{6,7} On day 8 the patient's blood pressure continued to remain stable, but physical examination revealed massive edema of the tongue, causing it to protrude outside of the mouth. The continuous infusion of nicardipine was discontinued and oral losartan 50 mg daily was added for further blood pressure control. Because the patient had previously taken valsartan without incident, it was decided that adding an ARB would not further aggravate her current condition.

On day 10, the clinical pharmacists conducted a detailed review of the patient's medication profile to assess possible drug-related causes of angioedema. The medications were examined for a temporal relationship between treatment initiation and onset of angioedema as well as for adverse effect profiles and case reports of similar reactions. Based upon this analysis, all medications were excluded with the exception of amlodipine and nicardipine, for which a relationship between the initiation of treatment and the onset of clinical signs and symptoms of angioedema was identified (Figure 1). As a result, amlodipine was discontinued on day 11. Approximately 24 hours later, physical examination showed a significant reduction in oropharyngeal and tongue edema, which continued to resolve through day 13. On day 13, oral diphenhydramine 25 mg every 6 hours, intravenous hydrocortisone 100 mg every 8 hours, and oral ranitidine 150 mg twice daily were initiated to alleviate the remaining swelling. The angioedema completely resolved by day 15, and the patient self-extubated on day 16.

The patient was transferred to the intermediate care unit on day 18; however, she developed new-onset seizures, tachycardia, and respiratory distress. Her neurologic and respiratory status continued to decline and on day 25 progressed to cardiac arrest; she was unable to be resuscitated.

Discussion

There are multiple proposed mechanisms for the development of angioedema, including allergic, genetic, idiopathic, medication-induced, physically induced (cold, heat, vibration, trauma), cytokine-associated, thyroid autoimmune disease-associated, and acquired.¹⁻³ An attempt was made to rule out all other potential causes of angioedema in our patient before drug-related causes were considered. The patient had no known personal or family history of an-

gioedema and no history of allergy to any of the medications administered during her hospital course. Complete blood cell count showed no eosinophilia and complement assays were lost due to a laboratory ordering error. Based on the patient's past history and normal thyroid-stimulating hormone level, she had no known thyroid disease. During the hospital course she was never exposed to extreme changes in temperature and did not undergo any surgical procedures.

Labetalol, famotidine, fosphenytoin, vancomycin, propofol, nicardipine, amlodipine, atropine, epinephrine, and fentanyl were evaluated for their possible risk of angioedema. The evaluation did not identify any case reports describing an association between any of these medications and angioedema. As previously stated, fosphenytoin and famotidine were discontinued on days 6 and 7, respectively. Frequent facial edema and infrequent tongue edema are listed as adverse effects in the package insert for fosphenytoin; however, the manufacturer has no additional case reports of these adverse reactions.⁶ Angioedema has been reported in the package insert for famotidine as an infrequent cause of hypersensitivity reactions; however, according to the manufacturer, there have been no additional case reports of hypersensitivity.⁷ Furthermore, a literature search on Ovid using MEDLINE (1950 to November 2008) provided no case reports of angioedema with these medications. As seen in Figure 1, signs and symptoms of angioedema continued to persist after discontinuation of fosphenytoin and famotidine for 7 days; based on this information these drugs were excluded as causes of our patient's angioedema. Labetalol was excluded as a cause because angioedema occurred 4 days after its discontinuation and the duration of labetalol use and cumulative dose were minimal (<3 h). In addition, there were no cases of labetalol-induced angioedema in the study conducted by Hedner et al.⁸ There are no known case reports of atropine or epinephrine inducing angioedema. There is no temporal relationship between these medications and our patient's angioedema due to their short half-life and the occurrence of swelling starting 5 days after their discontinuation (Figure 1). Vancomycin was continued throughout the course of angioedema and after angioedema had resolved. Vancomycin concentrations were followed throughout the patient's antibiotic course and were consistently therapeutic (goal 8–15 µg/mL). Case reports of cocaine-induced angioedema reported symptom onset within hours of administration and resolution within 9 hours of onset. In our patient, angioedema occurred on day 5 of admission and took 10 days to resolve. Based on this information, epinephrine, atropine, cocaine, and vancomycin were excluded as causes of angioedema.

CCB-induced angioedema has been reported in 7 patients receiving verapamil, diltiazem, or nifedipine. Romano et al.⁹ reported a 52-year-old male with a history of

type 2 diabetes mellitus and hypertension who received diltiazem 180 mg daily for angina. Two days after initiation, the patient was reported to have widespread maculopapular eruptions and facial edema. Diltiazem and metoprolol were discontinued and methylprednisolone was initiated; 11 days later the patient's symptoms had resolved. A second case in Romano et al.'s report involved a 75-year-old male with a history of ischemic heart disease presenting with a 48-hour history of rash. The patient had been taking oral isosorbide dinitrate and diltiazem 180 mg daily. Maculopapular rash on the face, trunk, and limbs, as well as facial edema and tongue swelling, were documented. After 2 days of treatment with methylprednisolone and discontinuation of diltiazem, the symptoms resolved. Both patients underwent allergy testing 2 months after the event using skin and patch tests with diltiazem, yielding a positive result for allergy.

Sadick et al.¹⁰ reported 2 cases of angioedema caused by diltiazem in women aged 56 and 62 years. Both women developed periorbital edema 1–2 months after the initiation of diltiazem; the edema resolved 48 hours after discontinuation of the drug. Sadick et al. also reported a third woman who developed periorbital edema and pruritic eruptions 2 weeks after the initiation of verapamil; the angioedema resolved within 72 hours of discontinuation. Lastly, Sauve et al.¹¹ reported 2 patients who received nifedipine 50 mg, resulting in angioedema. The details of this case report are not discussed here, as it was published in French.

There are several similarities between these case reports and our patient, such as the onset of symptoms within the first 7 days of therapy and significant improvement of angioedema within the first 48 hours of withdrawal of the offending agent.¹² Based on these similarities, nicardipine and amlodipine could have induced our patient's angioedema; however, symptoms of angioedema continued for 4 days after discontinuation of nicardipine. Amlodipine was initiated 24 hours before the onset of angioedema and symptoms began to improve 24 hours after discontinuation, suggesting a strong causal relationship between the drug and the disease. Furthermore, use of the Naranjo probability scale indicated a probable relationship between treatment with amlodipine and development of angioedema in our patient.¹³ Factors included the adverse event appearing after the suspected drug was given, adverse reaction improving upon discontinuation, no alternative causes resulting in this reaction, and confirmation of the adverse event by objective evidence. Unlike some of the previous case reports, this patient was never rechallenged with amlodipine or administered a skin test due to the patient's death on day 25 of the hospital stay.

The principal treatment of drug-induced angioedema is the discontinuation of the precipitating agent and management of the patient's airway. In this case, our patient's respiratory function stabilized and extubation was possible

once amlodipine was discontinued. Based on the available literature, angioedema symptoms usually resolve within 48–72 hours.¹² Despite lack of proven efficacy, hydrocortisone and ranitidine were initiated; however, this was 48 hours after discontinuation of amlodipine even though signs and symptoms of angioedema had already started to resolve.^{14,15}

ACE inhibitors are the most frequently reported causes of drug-induced angioedema and a potential mechanism has been proposed, although it remains unsupported. The proposed mechanism of ACE inhibitor-induced angioedema may result from the activation of the kallikrein–kinin system and classic complement pathway, leading to the release of bradykinin, kallidin, and anaphylatoxins. This pathway may increase vascular permeability and vasodilation, precipitating angioedema. This mechanism is thought to be related to an increase in kinins.^{2,16} ACE inhibitors increase kinin levels by preventing their breakdown; however, amlodipine also affects the kinin system by stimulating kinin formation through activation or release of kallikrein.¹⁷ In addition, the combined use of nicardipine, a strong CYP3A4 inhibitor, with amlodipine, a CYP3A4 substrate, may lead to a significantly increased serum concentration of amlodipine, potentially leading to an abnormal increase in kinin production.¹⁸

Although there is only a small body of case reports implicating CCBs as the cause of angioedema, amlodipine was the most likely cause of angioedema in our patient. Her past history revealed no adverse reactions associated with verapamil use; therefore, CCB-associated angioedema may not be considered as a class effect until more evidence on this topic is available. Clinicians should perform a comprehensive drug history review when faced with a case of angioedema and consider amlodipine as a probable cause of this potentially life-threatening reaction.

Jessica Southward PharmD, Postgraduate Year 2 Emergency Medicine Specialty Resident, Pharmacy and Drug Information, Grady Health System, Atlanta, GA

Elizabeth Irvine PharmD, Postgraduate Year 2 Hematology/Oncology Specialty Resident, Pharmacy and Drug Information, Grady Health System

Marina Rabinovich PharmD BCPS, Critical Care Specialist, Pharmacy and Drug Information, Grady Health System

Reprint: Dr. Southward, Pharmacy and Drug Information, Grady Health System, 80 Jesse Hill Jr. Dr., SE, Atlanta, GA 30303, fax 404/616-2228, jsouthward@gmh.edu

References

1. Agostoni A, Cicardi M. Drug-induced angioedema without urticaria. *Drug Saf* 2001;24:599–606.
2. Temino VM, Peebles RS. The spectrum and treatment of angioedema. *Am J Med* 2008;121:282–6.
3. Kaplan AP, Greavers MW. Angioedema. *J Am Acad Dermatol* 2005;53:373–88.
4. Losartan. DRUGDEX System. Greenwood Village, CO: Thomson Micromedex (accessed 2008 Oct 29).

5. Warner KK, Visconti JA, Tschampel MM. Angiotensin II receptor blockers in patients with ACE inhibitor-induced angioedema. *Ann Pharmacother* 2000;34:526-8. DOI 10.1345/aph.19294
6. Product information. Cerebyx (fosphenytoin). New York: Pfizer, June 2002.
7. Product information. Pepcid (famotidine). Deerfield, IL: Baxter Healthcare Corporation, June 2007.
8. Hedner T, Samuelsson O, Lindholm L, Andren L, Wiholm BE. Precipitation of angioedema by antihypertensive drugs. *J Hypertens* 1991;9: S360-1.
9. Romano A, Pietrantonio F, Garcovich A, et al. Delayed hypersensitivity to diltiazem in two patients. *Ann Allergy* 1992;69:31-2.
10. Sadick NS, Katz AS, Schreiber TL. Angioedema from calcium-channel blockers. *J Am Acad Dermatol* 1989;21:132-3.
11. Sauve L, Gras-Champel V, Decocq G, et al. Angioedema associated with the use of dihydropyridines (letter). *Therapie* 1999;54:64-5.
12. Chiu AG, Newkirk KA, Davidson BJ, et al. Angiotensin-converting enzyme inhibitor-induced angioedema: a multicenter review and an algorithm for airway management. *Ann Otol Rhinol Laryngol* 2001;110: 834-40.
13. Naranjo CA, Busto U, Sellers EM, et al. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther* 1981;30:239-45.
14. Reed LK, Meng J, Joshi GP. Tongue swelling in the recovery room: a case report and discussion of postoperative angioedema. *J Clin Anesth* 2006;18:26-9.
15. Frigas E, Nzeako UC. Angioedema pathogenesis, differential diagnosis, and treatment. *Clin Rev Allergy Immunol* 2002;23:217-31.
16. Pigman EC, Scott JL. Angioedema in the emergency department: the impact of angiotensin-converting enzyme inhibitors. *Am J Emerg Med* 1993;11:348-54.
17. Mason RP, Marche P, Hintze H. Novel vascular biology of third-generation L-type calcium-channel antagonists. *Arterioscler Thromb Vasc Biol* 2003;23:2155-63.
18. Nakamura K, Ariyoshi N, Iwatsubo T, et al. Inhibitory effects of nicardipine to cytochrome P450 (CYP) in human liver microsomes. *Biol Pharm Bull* 2005;28:882-5.

Posible Angioedema Inducido por Amlodipino

J Southward, E Irvine, y M Rabinovich

Ann Pharmacother 2009;43:772-6.

EXTRACTO

OBJETIVO: Notificar un caso de angioedema probablemente asociado con la administración de amlodipino en un paciente con ictus hemorrágico del tálamo derecho.

RESUMEN DEL CASO: Una mujer de 50 años presentó angioedema durante la hospitalización por un ictus hemorrágico del tálamo derecho. No presentaba un historial médico previo de angioedema y se evaluó el riesgo de todos los medicamentos. Tras una evaluación minuciosa, los informes del caso, que vinculan los bloqueantes de los canales del calcio (BCC) y

el angioedema, llevaron a la realización de exámenes adicionales del fármaco amlodipino. La terapia con amlodipino se inició 24 horas antes del desarrollo del angioedema, que se resolvió 72 horas después de su retirada. En total, la paciente experimentó hinchazón orofaríngea durante 10 días.

DISCUSIÓN: En nuestros esfuerzos por examinar una causa del angioedema, eliminamos las causas, genéticas, alérgicas, de origen físico, por enfermedades autoinmunes del tiroides y de tipo farmacológico. Seis informes de casos han relacionado los BCC; verapamilo, diltiazem, y nifedipino; con angioedema. El inicio y la resolución de los síntomas en este caso fueron muy similares al de otros informes de casos hallados en la literatura científica. La aplicación de la puntuación de probabilidad de reacciones farmacológicas adversas según la escala Naranjo halló una probable relación entre amlodipino y angioedema.

CONCLUSIONES: Aunque ya existían con anterioridad algunos informes de angioedema inducida por BCC, se trata del primer caso notificado que sugiere un enlace entre angioedema y la terapia con amlodipino. Los facultativos deben considerar el fármaco amlodipino como una causa potencial de angioedema.

Traducido por Enrique Muñoz Soler

Angioédème Probable Induit par l'Amlodipine

J Southward, E Irvine, et M Rabinovich

Ann Pharmacother 2009;43:772-6.

RÉSUMÉ

OBJECTIF: Rapporter un cas d'angioédème probablement associé à l'administration d'amlodipine chez un patient avec un accident cérébrovasculaire (ACV) hémorragique au niveau du thalamus droit.

RÉSUMÉ DU CAS: Une femme de 50 ans a développé de l'angioédème lors de son hospitalisation suite à une AVC hémorragique au niveau du thalamus droit. Elle nie toute histoire antérieure d'angioédème et tous ses médicaments ont été évalués pour le risque d'angioédème. Après une étude approfondie, les rapports de cas associant les antagonistes calciques et l'angioédème ont mené à évaluer l'amlodipine comme agent responsable. Ce dernier fut débuté 24 heures précédant le développement d'angioédème qui s'est résolu 72 heures après son arrêt. La patiente a développé de l'enflure oropharyngée durant une période totale de 10 jours.

DISCUSSION: Lors de notre recherche pour évaluer la cause de l'angioédème, nous avons éliminé les causes génétiques, allergiques, induites par un trauma, induites par une maladie auto-immune thyroïdienne et celles induites par les médicaments. Six rapports de cas ont lié les antagonistes calciques tels verapamil, diltiazem, et la nifédipine à l'angioédème. Le début et l'arrêt des symptômes de notre patiente furent similaires à ceux rapportés dans la littérature. L'application du score Naranjo a déterminé un lien probable entre l'amlodipine et l'apparition de l'angioédème.

CONCLUSIONS: Bien que peu de rapports de cas induits par les antagonistes calciques existent, ceci constitue le premier rapport suggérant un lien entre l'amlodipine et l'angioédème. Les cliniciens devraient considérer l'amlodipine comme cause potentielle d'angioédème.

Traduit par Marc M Perreault