Methylene Blue in the Treatment of Refractory Shock From an Amlodipine Overdose

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Amlodipine is a potent vasodilator with a long half-life and delayed onset of action that is particularly concerning after an overdose. Vasodilation occurs through stimulation of nitric oxide release with increased cyclic guanosine monophosphate (cGMP) production. Methylene blue inhibits guanylate cyclase. This enzyme is responsible for the production of cGMP. Methylene blue also has the ability to scavenge nitric oxide, as well as inhibit nitric oxide synthase. We report the use of methylene blue for refractory shock in a patient with amlodipine toxicity. [Ann Emerg Med. 2011;58:565-567.]

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INTRODUCTION

Calcium channel blocker overdose of toxicity account for a substantial portion of mortality from cardiovascular drugs. There are at least 10 different calcium channel blockers currently available in the United States, several of which are available in both immediate and extended-release formulations. All calcium channel blockers available in the United States block L-type voltage-sensitive calcium channels, which decreases influx of calcium into cells.[1] Death from large overdoses of verapamil or diltiazem is typically due to profound negative inotropy and chronotropy in the setting of vasodilation.

Dihydropyridines such as amlodipine and nifedipine exert their primary action on L-type calcium channels located in vascular smooth muscle. Dihydropyridines are less potent on L-type calcium channels located on cardiac tissue than either verapamil or diltiazem. Amlodipine has potent vasodilatory effects, a long half-life ranging between 30 and 60 hours, and delayed onset of action, which makes it particularly concerning in overdose where deaths have been reported.[2] Amlodipine toxicity often mimics vasodilatory shock similar to sepsis or anaphylaxis.[3-5] The vasodilatory shock caused by amlodipine can be refractory to multiple therapeutic modalities such as calcium, vasopressors, and high-insulin euglycemic therapy.[3-5]

We report a case of severe amlodipine overdose that was refractory to conventional therapy but improved after administration of methylene blue.

CASE REPORT

After an argument with her boyfriend, a 25-year-old, 60-kg woman with no medical history presented to the emergency department 60 minutes after an ingestion of 40 tablets of amlodipine (10 mg) (there were no other cardioactive medications present). Initial vital signs were blood pressure 120/86 mm Hg, pulse rate, 110 beats/min; respiratory rate 13 breaths/min; oral temperature, 36.6°C (98°F); room air pulse oximetry, 98%. Her mental status was normal, with depressed affect. The general physical examination was normal, with no focal findings. An ECG demonstrated sinus tachycardia, with normal axis and intervals. Laboratory studies included a normal CBC count and chemistry panel. Both acetaminophen and salicylates were nondetectable in her serum.

The patient received an oral dose of activated charcoal at 1 g/kg on presentation. Approximately 2 to 3 hours after her ingestion, the patient became hypotensive, with a blood pressure of 75/40 mm Hg, and her pulse rate increased to 120 beats/min. During 3 hours, the patient received intravenously a total of 3 L of normal saline solution, 40 mL of 10% calcium gluconate, and 10 mg of glucagon, with no improvement. About 7 hours postingestion, dopamine at 5 μg/kg per minute was started, followed by norepinephrine at 1 μg/minute. Despite these therapies, the patient's blood pressure and pulse rate remained unchanged, but her mental status was preserved. A repeated ECG result unchanged.

Approximately 8 hours postingestion and after consultation with the poison center, 30 mL of 10% calcium gluconate and high-dose insulin-euglycemia therapy (1 unit insulin/kg bolus, followed by an infusion of 0.5 to 1.0 units/kg per hour) was administered. Repeated vital signs 1 hour after administration of the above recommendations were blood pressure 75/40 mm Hg and pulse rate 110 beats/min. She received high-dose insulin-euglycemia for a total of 8 hours without developing hypoglycemia. At this time, the patient became confused, which was soon followed by lethargy, and she underwent tracheal intubation with etomidate 20 mg and succinylcholine 120 mg. An arterial blood gas showed pH 7.23, PCO_2 40 mm Hg, PO_2 310 mm Hg, HCO_3– 16 mEq/L, and

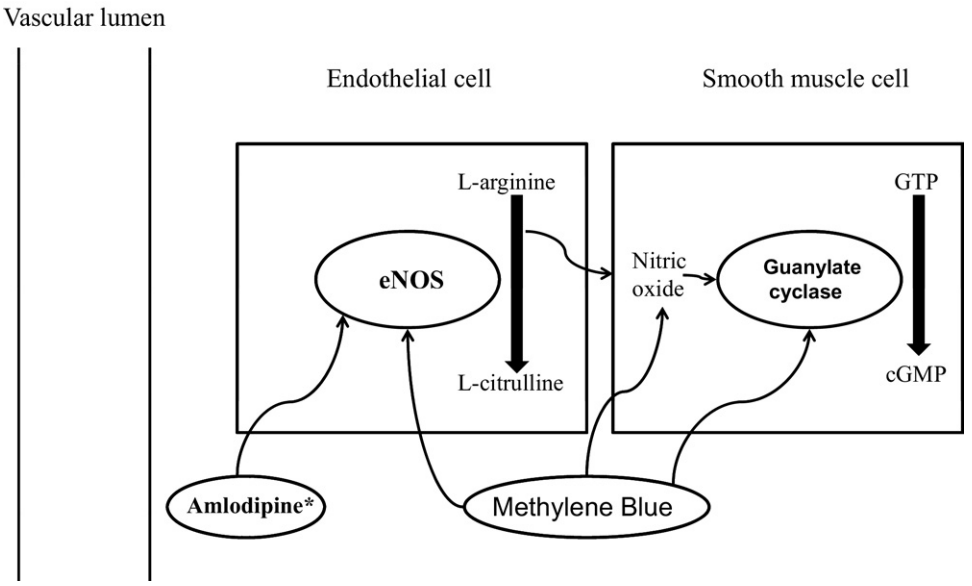

Figure. Amlodipine may cause inappropriate vasodilation by increasing the concentration of nitric oxide through stimulation of endothelial nitric oxide synthase. Methylene blue has several actions that may counteract the effect of increased nitric oxide synthase stimulation. First, it may antagonize endothelial nitric oxide synthase activity. Furthermore, it may scavenge nitric oxide directly and inhibit guanylate cyclase activity. Inhibition of guanylate cyclase results in decreased cyclic GMP (cGMP), which can increase the response to vasoconstrictor drugs and decrease vasodilation caused by excessive cGMP. *eNOS*, Endothelial nitric oxide synthase; *GTP*, Guanosine-5-triphophate.
*This is in addition to blockade of L-type calcium channels.

lactate 4.1 mmol/L. The patient was transferred to the ICU, where she remained hypotensive.

A bedside transthoracic echogram demonstrated a hyperdynamic left ventricle with no appreciable effusions and a normal inferior vena cava. A right-sided heart catheterization showed that the pulmonary capillary wedge pressure was 16 mm Hg (normal 2 to 10 mm Hg), cardiac index 5.1 L/min/m^2 (normal 2.5 to 4.2 L/min/m^2) and systemic vascular resistance of 400 dyne·sec/cm^5 (normal 700 to 1,600 dyne·sec/cm^5). She ultimately received high-dose insulin-euglycemia therapy with insulin infusion rates as high as 2 units/kg/hour, dopamine as high as 15 μg/kg/min a, and norepinephrine at 10 μg/minute, with little improvement for more than 14 hours after her ingestion.

At 16 hours postingestion, methylene blue was recommended by the poison center and administered at 2 mg/kg during 20 minutes, followed by an infusion of 1 mg/kg/hour. One hour after initiation of this regimen, the patient's blood pressure increased to 90/75 mm Hg and her pulse rate decreased to 90 beats/min. She was eventually weaned off all pressors and high-dose insulin-euglycemia, and methylene blue was discontinued. The patient was discharged without any sequelae 6 days later. The patient's serum concentration determined on blood from admission was 36 μg/mL (therapeutic range 3 to 10 μg/mL).

DISCUSSION

Experimental studies have demonstrated a vasodilatory effect of some calcium channel blockers that results from increased stimulation of nitric oxide release. A study demonstrated that amlodipine but not nifedipine or diltiazem stimulated synthesis of nitric oxide (measured as an increase in nitrite) in a dose-dependent fashion from canine coronary microvessels.[6] In a follow-up study, the same authors found that the *R*+ enantiomer of amlodipine is responsible for increased synthesis of nitric oxide, whereas the *S*− enantiomer resulted only in blockade of L-type calcium channels, with no release of nitric oxide.[7] Although the exact mechanism is uncertain, amlodipine may stimulate nitric oxide by increasing endothelial nitric oxide synthase activity through phosphorylation, as well as mediation of bradykinin B_2 receptors.[8,9]

Nitric oxide synthase also plays an important role in regulating vascular tone (Figure). There are 3 isoforms of nitric oxide synthase: neuronal, inducible, and endothelial. Nitric oxide in blood vessels is produced by endothelial nitric oxide synthase and is involved with regulating vascular function.[10] Nitric oxide in vascular smooth muscle is produced by inducible nitric oxide synthase, as well as cardiac myocytes, by mediators such as tumor necrosis factor, various cytokines, and oxidative stress. Activation of either nitric oxide synthase isoform results in an increased production of nitric oxide, which then increases the generation of cyclic guanosine monophosphate (cGMP) by activation of guanylate cyclase.[10] The accumulation of cGMP leads to vasodilatation and decreased systematic vascular resistance, as well as decreased contractile response to vasoconstrictors such as norepinephrine. This mechanism may also explain why severe amlodipine toxicity is resistant to treatment.

Methylene blue decreases cGMP through inhibition of guanylate cyclase, scavenges nitric oxide, and inhibits nitric oxide synthesis. Inhibition of excessive production and activity of both nitric oxide and cGMP may be critical in the treatment of refractory vasodilatory shock that occurs in cardiac bypass, sepsis, and anaphylaxis.[11]

Although work with nonspecific competitive nitric oxide synthase inhibitors such as *N*-monomethyl-L-arginine demonstrated an increased mean arterial pressure in sepsis, no mortality benefit has been demonstrated.[12] In fact, the use of nonspecific nitric oxide synthase inhibitors has resulted in increased mortality in both animal and humans.[12,13] This may partly be because nitric oxide is also vital in many other important pathways, so nonspecific inhibition of nitric oxide synthase can be detrimental. Subsequent studies evaluated inhibition of inducible nitric oxide synthase and targeting the actual production of cGMP by inhibiting soluble intracellular enzyme guanylate cyclase.

The literature that reports the use of methylene blue in vasodilatory shock from sepsis is primarily limited to retrospective case series and case reports.[14,15] Other studies also demonstrate decreased vasopressor requirement, as well as an increase in systemic vascular resistance.[16,17] Other animal models of sepsis that use methylene blue have shown a hemodynamic benefit across different animal species as well.[18,19]

One of the limitations of our case is that we could not completely exclude other potential agents such as other calcium channel blockers and β-blockers. Another limitation is whether methylene blue truly had a therapeutic effect. Although it is possible the patient's clinical status would have improved without the use of methylene blue, we believe it may have contributed to her improvement because her hemodynamics improved soon after the administration of methylene blue.

Calcium channel blocker overdoses are associated with high morbidity and mortality. In some cases, death occurs despite therapeutic options such as high-insulin euglycemic therapy, intravenous fat emulsion therapy, and invasive modalities such as intra-aortic balloon pump. Methylene blue may be a new antidotal treatment for refractory vasodilatory shock from dihydropyridine overdoses. It is available in most hospitals, inexpensive, and has a relatively favorable adverse effect profile and should be considered after traditional treatments for calcium channel blocker overdoses have been exhausted.

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