Anaphylaxis with *Latrodectus* Antivenin Resulting in Cardiac Arrest

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Abstract *Latrodectus mactans* antivenin is a safe and effective therapy for severe black widow spider envenomations when given to most patients. We report a case of a 37-year-old male with a history of asthma that was given *L. mactans* antivenin for symptoms related to a black widow envenomation and developed a severe anaphylactic reaction resulting in cardiac arrest. When traditional therapies failed, the patient was given methylene blue for anaphylactic shock resulting in a 30-h period of hemodynamic stability. Despite initial resuscitation, the patient ultimately died 40 h after presentation. Under the right circumstances, *L. mactans* antivenin remains a safe and effective therapy for severe black widow envenomations. However, anaphylaxis is a risk for those receiving this therapy, even when the antivenin is diluted and given as an infusion. We report the first death related to diluted *L. mactans* antivenin given as an infusion.

Keywords Black widow · Antivenin · Anaphylaxis · Methylene blue · *Latrodectus mactans*

Introduction

Black widow envenomations are common but rarely fatal in the USA. On review of the last 11 years of published poison center data, there were an average of 2,500 bites per year with no reported fatalities [1–11]. Mainstays of therapy include opioids, muscle relaxants, and *Latrodectus mactans* antivenin. On query of reported cases to the National Poisoning Data System of all human envenomations from *L. mactans* between 2000 and 2009, there were 25,702 reported envenomations of which 554 (2.16%) received *L. mactans* antivenin [personal communication with Dr. A Bronstein, August 2011]. The antivenin is very effective at improving symptoms related to the envenomation. The biggest complication with administration of antivenin is anaphylaxis, as it is comprised from partially purified horse serum. When it occurs, *L. mactans* antivenin-induced anaphylaxis usually responds to traditional therapies: steroids, epinephrine, and antihistamines. To date, only one *L. mactans* antivenin-associated death has been previously reported in the literature [12]. In this case, the patient had a severe anaphylactic reaction resulting from the administration of undiluted *L. mactans* antivenin given as an intravenous bolus [12].

Case Report

A 37-year-old male presented to an emergency department 3 h after sustaining a self-confirmed black widow spider bite to the right lower extremity. Approximately 1 h later, he developed tightening in his neck and shoulders that was associated with some nausea and diaphoresis. His only medical history was asthma, and he used an albuterol

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metered-dose inhaler and fluticasone propionate/salmeterol inhalation powder, as needed.

Initial vital signs were temperature of 98.5°F, blood pressure of 159/74 mmHg, pulse ox 96% on room air, respiratory rate of 22 respirations per minute, and heart rate of 103 beats per minute. Physical exam demonstrated a man in moderate distress with a small area of raised erythema on his right anterior mid-shin. He had no diaphoresis and his abdomen was soft and non-tender with no peritoneal signs.

Symptomatic relief was attempted, but not achieved, with one intravenous (IV) dose of 30 mg ketorolac and two IV doses of both 1 mg lorazepam and 1 mg hydromorphone. The patient was given a subcutaneous test dose of normal horse serum in saline, as directed by *L. mactans* antivenin package insert, with no reaction. An infusion of 2.5 mL of antivenin in 50 mL of 0.9% normal saline was started. Five minutes after the antivenin infusion was started (10% infused), he developed symptoms of anxiety, facial tingling, shortness of breath, tachycardia to 135 beats per minute, and tachypnea to 36 breaths per minute with a decrease in his oxygen saturation to 89% on room air. The antivenin infusion was stopped, but cardiac arrest occurred within 3 min.

He was intubated, given multiple doses of epinephrine, as well as diphenhydramine, naloxone, and methylprednisolone. Nebulized albuterol was administered when he became difficult to ventilate manually and wheezing was noted. Thirty minutes after arrest, the patient had return of spontaneous circulation (ROSC). He was started on a dopamine infusion for persistent hypotension and quickly exceeded maximum dosing (30 µg/kg/min). Subsequently, phenylephrine was started and rapidly increased to 126 µg/min. The patient went into cardiac arrest for a second time and standard ACLS therapies were performed, including administration of calcium chloride and sodium bicarbonate. The patient had ROSC 20 min later and made purposeful movements. Arterial blood gas (ABG) 20 min after ROSC demonstrated acidosis (pH 6.934) and carbon dioxide retention (pCO₂, 86.8 mmHg) (Fig. 1). He was given fentanyl and vecuronium to resedate and paralyze him and was transferred to a tertiary care center. Despite being on high doses of phenylephrine, vasopressin, dopamine, norepinephrine, and epinephrine drips, he remained hypotensive with blood pressures ranging from 84/75 to 104/89 mmHg (Table 1). He continued to have myoclonic jerking of shoulders, neck and arms, his pupils were fixed and dilated, and he developed oliguria. ABG demonstrated continued acidosis (pH 6.931) and carbon dioxide retention (pCO₂, 100 mmHg) despite a ventilator rate of 25. A bolus dose of 1 mg/kg of methylene blue was given intravenously. Within 45 min, the dopamine, phenylephrine, norepinephrine were discontinued and the epinephrine decreased to 2.6 µg/kg/min. Epinephrine and vasopressin were discontinued within 85 min of the methylene blue bolus, and ABG also

demonstrated improved respiratory function with pH of 7.119 and pCO₂ of 44.1 mmHg. The patient improved significantly over the next 12 h and was noted to be following commands and attempting to get out of bed while still intubated. The primary physician reported the patient “seemed to have avoided major anoxic brain injury; serial labs have shown improvement in academia but metabolic acidosis still significant enough to preclude extubation. We should be able to extubate him tomorrow.”

During the night of hospital day 2, the patient developed a temperature of 101.6°F, his blood pressure dropped from 121/83 to 54/35 mmHg, and his oxygen saturation abruptly decreased to 80% with an FiO₂ of 45%. A venous blood gas was performed while manually ventilating the patient pH 6.99, pCO₂ of 71 mmHg, pO₂ of 10 mmHg, and oxygen saturation of 5%. Thirty minutes later, he was restarted on norepinephrine, went into cardiac arrest and expired approximately 40 h after initial presentation.

An autopsy was not performed. The medical examiner attributed the cause of death to anaphylactic shock secondary to administration of antivenin based on review of the medical record and external viewing only. No angioedema or rashes were noted in the medical examiner's report. Given the clinical course and that deep vein thrombosis prophylaxis was intentionally withheld, it is more likely the patient died of a pulmonary embolism as a complication from his antivenin-induced anaphylactic shock and cardiac arrest. His marked and sustained improvement for 30 h followed by his sudden death without recurrence of anaphylactic symptoms supports this.

Discussion

Black widow spiders, *L. mactans*, are native to North America, and symptoms related to their bites are caused by the venom component, α-latrotoxin [12]. Alpha-latrotoxin binds to presynaptic receptors neuroligin I-α and latrophilin initiating a cascade of events that leads to neurotransmitter release from the presynaptic nerve into the synapse. The result is excessive motor end plate stimulation [13]. Some of the resulting clinical effects include muscle spasm, localized diaphoresis, piloerection, and hypertension [14]. Bites usually occur on an extremity and may or may not be accompanied by a stinging sensation. A period of 10–60 min may pass before other symptoms develop [15–17]. Shoulder, back, chest, and abdominal pain often develop as the venom effect moves proximal to the bite site. There may be a marked feeling of restlessness, but intractable pain is the major complaint of *Latrodectus*-envenomated patients. The majority of symptoms peak during the first 48 h after envenomation and decline within 2–3 days. Symptoms may persist up to 7 days; however, generalized

Fig. 1 Blood gas values vs. time after presentation. All values are from arterial blood gases with the exception of values at hour 39 which are from a venous blood gas. Solid arrows indicate active cardiac arrest; open arrow indicates time of methylene blue administration

weakness, muscle pain, and malaise may last for weeks [12, 16–19]. A grading scale has been developed to assist assessment of symptom severity (Table 2) [20].

Although several treatment regimens have been used, parenteral opioids and *L. mactans* antivenin (Antivenin®; Merck & Co., Inc, Whitehouse Station, NJ, USA) are most successful in treating the signs and symptoms of severe *Latrodectus* envenomation. *L. mactans* antivenin alone was found to shorten the course of illness for severely envenomated patients (grades 2 and 3) when compared to opioids in a retrospective study by Clark and colleagues [20]. *L. mactans* antivenin is very effective at relieving acute pain and resolving systemic symptoms, and its administration up to 90 h post-envenomation has been associated with clinical resolution of symptoms [21, 22]. Current recommendations for when to give antivenin

include grades 2 or 3 envenomations, envenomations refractory to opiates and sedative hypnotics, patients suffering from rare effects such as priapism, and pregnant patients at risk for miscarriage due to latrodectism-related muscle cramping and hypertension [15, 23, 24]. However, a recently published review found no change in fetal outcome in pregnant women whose treatment included black widow spider antivenin and those who were treated with other medications calling this last indication into question [25]. Some early sources, including the *L. mactans* antivenin package insert, recommend giving this therapy to all envenomated patients at the extremes of age [15, 23, 26]. The only contraindication listed is an existing horse allergy or previous exposure to horse serum [23]. Interestingly, both our patient and the *L. mactans* antivenin-related death reported by Clark had medical histories of asthma [12, 23].

Antivenins are hyperimmune sera containing antibodies, usually IgG, collected from animals after inoculation with a target venom. *L. mactans* antivenin is a partially purified equine-derived IgG used to treat envenomations from multiple *Latrodectus* species due to similarities in venoms [27]. Acute hypersensitivity reactions occur with exposure to animal proteins and whole immunoglobulins within the antivenin. Most of the data used to determine the risk for developing hypersensitivity reactions to *L. mactans* antivenin is extrapolated from experience with another horse serum-based antivenin, Antivenin Crotalidae Polyvalent (ACP; Wyeth Laboratories, Philadelphia, PA, USA). Reports indicate that 10–39% of patients receiving ACP developed immediate hypersensitivity reactions [28, 29]. As the overall amount of ACP used to neutralize snake venom is much larger than the amount of *L.*

Table 1 Vasopressor use at given time points after presentation

Time after presentation (hours)	Medication and dose given
9.5	Norepinephrine 10 µg/kg/min Phenylephrine 70 µg/min Epinephrine 11 µg/min Dopamine 12 µg/kg/min Vasopressin 0.04 units/minute
9.75	Methylene blue 1 mg/kg bolus All vasopressors continued as noted above
10.5	Vasopressin 0.04 U/min Epinephrine 2.6 µg/min
11	All vasopressors off

Table 2 Severity grading scale for *Latrodectus mactans* envenomation. Adapted from Clark et al. [20] and Hoover and Fortenberry JD [24]

Grade of envenomation	Signs and symptoms
1 Mild	Normal vital signs Asymptomatic Local pain at envenomation site
2 Moderate	Normal vital signs Muscular pain in envenomated extremity Extension of muscular pain to abdomen if envenomated on lower extremity or chest if envenomated on upper extremity Local diaphoresis of envenomation site or involved extremity
3 Severe	Abnormal vital signs Hypertension (systolic blood pressure >140 mmHg or diastolic blood pressure >90 mmHg) Tachycardia (pulse >100) Generalized muscular pain in back, abdomen, and chest Diaphoresis remote from envenomation site Nausea and vomiting Headache Rare effects such as priapism

mactans antivenin used to neutralize black widow spider venom, the use of ACP data to predict the rate of anaphylaxis and immediate hypersensitivity may overestimate the frequency of these events. However, anaphylaxis remains the most severe complication of *L. mactans* antivenin.

To determine which patients may develop hypersensitivity to antivenin, skin testing is often implemented prior to antivenin administration in the USA and is recommended by the *L. mactans* antivenin manufacturer [14, 23]. However, several studies have reported the inaccurate prediction of the skin testing and challenged the usefulness of this practice. In one study of 25 patients from Nigeria and Thailand, 12 (48%) had negative skin and conjunctival tests, yet developed anaphylactic reactions when treated with equine-derived snake antivenoms [30]. All 23 patients receiving ACP in the case review by White and Weber had negative skin testing, but despite this, 13 (56%) developed “adverse reactions to antivenin” [29]. In an additional report, four of five patients (80%) who responded “unfavorably” to intravenous ACP had negative skin tests [31]. As it is unreliable and delays treatment, we believe skin testing should be abandoned.

The best method of minimizing the risk and severity of immediate hypersensitivity may be administration of diluted antivenin by means of a slow infusion. Rapid infusion has been associated with an increased number

of patients experiencing flushing, nausea, or anxiety [31]. Additionally, in the only other previously reported case of death related to *L. mactans* antivenin administration, undiluted antivenin was given as a bolus dose over a very short period of time [12]. Rapid administration of the antivenin may induce a massive histamine release causing anaphylactic signs and symptoms in patients [20]. Although severe reactions may not be prevented by slower infusion, this may limit the immediate anaphylactoid hypersensitivity reactions. Based on their experience, both Clark et al. and Merck recommend diluting the antivenin with 50–100 mL of normal saline or 5% dextrose (Clark et al.) or 10–50 mL of normal saline (Merck) and infusing the reconstituted solution over 15–30 min [12, 20, 23]. Pre-medication with antihistamines, steroids, or epinephrine has not been shown to prevent or decrease the frequency of these reactions. When anaphylaxis does occur, the infusion should be stopped immediately and patients should be treated with standard therapies: antihistamines, steroids, and epinephrine. Based on our experience with this case and a review of the literature, we would also recommend consideration of using methylene blue if standard therapies fail to reverse anaphylactic shock.

Methylene blue has been used over the last several years as a treatment for intractable hypotension in anaphylaxis, sepsis, and vasoplegia from cardiopulmonary bypass during cardiac surgery [32–35]. Multiple case reports document the reversal of anaphylactic symptoms, including drug-induced cardiac arrest and angioedema, after patients receive methylene blue [36–38]. Methylene blue inhibits soluble guanylyl cyclase, preventing vasodilation and decreasing associated vascular permeability by limiting the effect of nitric oxide [32, 36]. Evora and several others report rapid improvement of several patients who failed standard therapy with epinephrine, antihistamines, and steroids after developing hypotension with or without associated angioedema [36–38]. Reactions were induced by a variety of agents including intravenous contrast dye, penicillin and unknown agents. A dosing of 1.5–2 mg/kg IV bolus was given followed by infusions of 1.5–2 mg/kg/hr over 1–2 h [36–38]. Given our success along with others in treating anaphylactic shock with methylene blue, coupled with a rational biochemical mechanism for benefit, we believe methylene blue should be considered when standard treatments fail to reverse antivenin and possibly drug-induced anaphylaxis.

Conclusion

While *L. mactans* antivenin is very effective, physicians should be wary of using this antivenin without first exhausting traditional means of symptom control in patients

with contraindications. Based on this case and the previously reported death, we would propose asthma should be a contraindication to receiving *L. mactans* antivenin. Additionally, this case reinforces that skin testing is not sufficient to exclude potential allergic reactions and should be abandoned. Although our patient eventually succumbed, the initial resuscitation was successful only after the addition of methylene blue, thus supporting the use of methylene blue in anaphylactic shock when standard therapies fail. To our knowledge, this is only the second death related to black widow antivenin reported in the literature, and it is the first reported death attributed to *L. mactans* antivenin when diluted and infused over an extended period of time.

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