

ARTICLE

Examination of adverse events following black widow antivenom use in california

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Objectives. Following widow spider (*Latrodectus sp.*) envenomation, local pain, erythema, abdominal pain, rigidity, hypertension, and diaphoresis can be seen. While an effective specific antivenom (AV) is available, its use is limited due to concern of possible severe allergic reaction. We performed the current study to determine rate of adverse effects and the efficacy of AV in patients treated for widow spider envenomation. **Methods.** Observational case series of the California Poison Control System electronic database from January 1999 to December 2009. All cases of widow spider envenomation treated with AV were included. Age, gender, signs, and symptoms, adjunctive therapy, number of vials of AV given, and adverse reaction to AV were recorded. Descriptive statistical methods were used. **Results.** Ninety-six patients received AV, mean age 26 years (0.12–74 years), 76% male. Following widow spider envenomation generalized pain was reported in 91%, erythema at site in 57%, hypertension ($\geq 140/90$ mmHg) in 43%, muscle rigidity/cramping in 43%, abdominal pain in 41%, tachycardia (≥ 100 bpm) in 23% and diaphoresis in 21%. No patient required more than one vial of AV. One patient developed urticaria to AV halfway through infusion which was immediately discontinued. Another patient developed generalized flushing following completion of infusion but had no other effects. Two other patients reported myalgia and paresthesia. There were no deaths in any patients receiving AV. There was no shortness of breath or respiratory distress, no hypotension or chest pain following AV administration. All patients reported pain relief with AV and did not require additional AV doses. **Conclusions.** Our results suggest that Black Widow Spider Antivenin® (Merck) administration is relatively safe with mild to moderate adverse effects seen in only a small percentage of patients. There were no deaths, or severe allergic reactions identified. The retrospective use of poison control system data is a limitation of our study. Further prospective studies are needed to validate our findings and elucidate the full safety profile on this antivenom.

Keywords Antivenom, Antivenin, Spiders

Introduction

Currently, there is one commercially available widow spider antivenom in the United States, Black Widow Antivenin® (Merck), which has been available in the United States since 1954.¹ This is a lyophilized horse serum-derived product containing IgG antibodies against *Latrodectus mactans* venom. In 2009, there were 2302 *Latrodectus sp.* exposures reported to the American Association of Poison Control Centers (AAPCC) National Poison Data System.² It is estimated that approximately 200 vials will be ordered from the manufacturer in 2011 for confirmed bites. It is unknown whether the antivenom was actually administered to patients.¹

Black Widow Antivenin® (Merck) is currently on allocation from the manufacturer. This means for the time being

the manufacturer will supply an emergency supply of one package for patients with a suspected bite by a widow spider as a short-term solution to the current manufacturing shortage rather than have pharmacies restock their supplies.³ This is to ensure that patients in emergency need of the product will be able to obtain the antivenom.³

Reported adverse reactions in the manufacturer's package insert include: muscle cramps, hypersensitivity reactions including anaphylaxis and serum sickness.⁴ There is only one published report of death following administration of Black Widow Antivenin® (Merck).⁵ The manufacturer is not aware of any additional cases of death associated with their antivenom use.¹ As no deaths have been reported in the United States following widow spider envenomation alone, many clinicians are reluctant to administer the antivenom for concern of potential severe allergic reactions. There are two cases of death in the worldwide literature directly attributed to widow spider envenomation although these are not well described.^{6,7} Despite the concern of adverse effects with Black Widow Spider Antivenin® (Merck), there is a paucity of data addressing the safety of this product.

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The objective of our study is to determine the incidence and types of adverse effects following the administration of Black Widow Spider Antivenin® (Merck) in symptomatic widow spider envenomation.

Methods

Study design

Our study is an observational case series of the California Poison Control System (CPCS) electronic database (Visual Dotlab®) and was approved by the University of California, San Diego human research committee. The CPCS covers the entire state of California with a population of approximately 37 million people.

Study setting and population

The study period was from January 1, 1999 to December 31, 2009. Only cases identified as black widow envenomation occurring in humans and where black widow antivenom was administered were identified. All potential widow spider envenomation reported to the CPCS are encoded to a single generic code number. This allowed identification of all potential CPCS charts for review. The administration of antivenin was denoted in the notes section of record and also by coding a check box of therapies given. Once identified all the text notes were reviewed for text data for inclusion. All patients received Black Widow Antivenin® (Merck). No other antivenoms were administered. The CPCS recommends administering the antivenom as per the manufacturer's package insert. All patients were routinely followed while in the health care facility by the CPCS but not at defined intervals.

Inclusion criteria: any symptomatic patient given black widow antivenom for the treatment of acute widow spider envenomation. Cases in which antivenom was recommended by the CPCS but not actually administered were excluded. Only patients with a known outcome and complete poison center records were included in the final analysis. Exclusion criteria: no black widow antivenom administration, incomplete documentation, nonhuman (i.e. animal) cases. The study data were collected from the CPCS charts and abstracted directly into a standardized Microsoft Excel 2003 (Microsoft, Redmond, WA) spreadsheet.

Measures

Data elements extracted included: age, gender, and signs and symptoms following envenomation: local reaction (e.g. erythema or "target lesion"), abdominal pain, muscle cramping/muscular rigidity, tachycardia (defined as heart rate > 100 bpm), hypertension (defined as systolic blood pressure $\geq$ 140 mmHg or diastolic blood pressure > 90 mmHg), diaphoresis, and presence of generalized pain. The total number of vials of antivenom administered, and adjunctive medications administered (e.g. benzodiazepines, opioids). In addition, adverse reactions to antivenom administration were abstracted.

Data analysis

Descriptive statistical analysis was performed on all data.

Results

One hundred and five patients received antivenom. Nine patients were excluded due to incomplete records. There were 96 patients who met inclusion criteria of which, 73 (76%) were male and 23 (24%) female. The mean age of patients was 26 years with a range of (SD $\pm$ 18.53 years, 6 weeks–74 years). Forty-two percent were pediatric patients (18 patients less than 6 years, 22 patients were 6–18 years). All patients were evaluated and treated in a health care facility.

The signs and symptoms reported included: generalized pain 87 patients (91%), local reaction (erythema) 55 (57%), hypertension ($\geq$ 140/90 mmHG) 41 (43%), muscle cramping/rigidity 41 (43%), abdominal pain 39 (41%), tachycardia (> 100 bpm) 22 (23%), and diaphoresis 20 (21%). Adjunctive therapies included: opioids 75 patients (78%), benzodiazepines 69 (72%), calcium gluconate 23 (24%), nonsteroidal anti-inflammatories 18 (24%), and skeletal muscle relaxants 12 (13%).

All except one patient received one vial of antivenom. All patients reported pain relief with antivenom and no patients required additional doses of antivenom. The exact time to pain relief and initial pain scores (i.e. 1–10) were not able to be determined. The majority of patients (78%) also received opioid analgesics. All of these patients reported pain relief after antivenom administration. All patients received the entire dose of antivenom (i.e. one vial) except one patient whose infusion was stopped after half the dose with the onset of urticaria. The patient receiving the half dose reported pain relief.

Four patients (4%) had adverse effects ascribed to the antivenom administration. This was determined by either treating physician or poison center specialists and denoted in the CPCS record. Reported adverse effects included myalgias and "fatigue" in a 65-year-old man. This patient was observed in the emergency department for several hours and then discharged to home. A 26-year-old female described generalized paresthesias throughout her body following the infusion but had no motor weakness or any other adverse effects. This patient was admitted overnight and discharged the following day. The exact duration of the generalized paresthesias is unknown but suggested to be brief in record. Generalized flushing was seen in a 30-year-old man but he had no other complications. A 24-year-old man developed an urticarial rash halfway through infusion. The infusion was immediately stopped and no other signs or symptoms developed. Both of these two latter patients were treated symptomatically with diphenhydramine, admitted for observation, and discharged the following day. There were no cases of shortness of breath, bronchospasm, angioedema, hypotension, or death seen following antivenom administration. All patients were followed to discharge from either the emergency department, ED or the hospital. It is unclear if any patients had a recurrence of symptoms following discharge as we only identified patients given antivenom.

Discussion

The incidence of adverse reactions resulting from the use of antivenom in our study was low. There were no cases of respiratory compromise or anaphylaxis. Observed adverse effects were reported in only 4 patients (4%). One patient had an urticarial rash and another flushing of the skin. Recently, a case of urticaria, pruritis, and bronchospasm was reported in a 12-year-old male following administration of the antivenin.⁸ The paucity of other cases in the medical literature suggests a relatively safe adverse effect profile.

One patient in our study reported myalgias and "fatigue" immediately after the antivenom infusion. It is unclear if these effects were truly from the antivenom, as the time course and symptoms are not consistent with serum sickness reaction as developed soon after the completion of the antivenom infusion. Serum sickness, a type III hypersensitivity reaction, can be seen 7–21 days after the administration of antivenoms.⁹ Furthermore, variables including venom load, type and dose of antivenom, and specific antigens may play a role in the development of serum sickness. Both the venom load delivered and the dose of antivenom administered are small in widow spider envenomation. We cannot accurately comment on the incidence of serum sickness in our study patients as we did not follow them after discharge. No deaths were seen with antivenom use in our study. According to the manufacturer, controlled clinical studies for safety and effectiveness in children have not been conducted.⁴ Interestingly, 42% of our patients were less than 18 years of age and none had any reported adverse reactions.

Currently, there is one commercially available Black Widow Spider Antivenin[®] (Merck) available in the United States, which can rapidly reverse widow spider envenomation. At the time of the writing of this article, the average wholesale price (AWP) acquisition cost of one vial of Black Widow Spider Antivenin (Merck) is \$33.25.¹⁰ This low cost suggests it is a potentially cost-saving therapy. The antivenom seems to be particularly useful in patients refractory to supportive care alone.^{11–13} As the antivenom is a whole IgG product, there is a concern for severe allergic reactions (e.g. anaphylaxis) and serum sickness. Serum sickness, however, is usually dose dependent and is unlikely as generally only one or two vials of antivenom are administered.

In Australia, an equine-derived antivenom to the Red Back Spider (*Latrodectus hasselti*) is commercially available.¹⁴ Both *in vitro* and *in vivo* (mice) studies have demonstrated efficacy of this antivenom in neutralizing *L. mactans* and *L. Hesperus* venom.^{15,16} However, this product is not commercially available in the United States. There is an ongoing Phase III trial in the United States of an equine-derived widow spider antivenom, Antivenin Latrodectus (Black Widow) (Analatro[®]). As this is a F(ab)2 immunoglobulin product rather than whole IgG, it may be a safer alternative to the current available antivenom in the United States.¹⁷ However, as no clinical data has been reported and true incidence has yet to be determined. The current crotalidae polyvalent immune antivenom, an ovine-derived Fab fragment, has

been reported to have lower incidence of adverse reactions compared to the whole IgG crotalid antivenom.¹⁸ Similarly, the newly approved centruroides (Scorpion) (Anascorp[®]) is an equine F(ab)2 and according to the manufacturer after treatment of approximately 1800 patients in clinical studies the incidence of acute and delayed hypersensitivity reactions is less than 1%. This product has a similar protein content as their Latrodectus (Black Widow) (Analatro[®]) F(ab)2 antivenom.¹⁹

Despite the current antivenom being available since 1954 in the United States there is only one published report of death following administration of Black Widow Antivenin[®] (Merck).⁵ A detailed review of this single case identified the antivenom was undiluted and given by intravenous push rather than slow intravenous infusion to an atopic and asthmatic patient with multiple drug allergies.²⁰ This may have precipitated the severe acute allergic reaction. Furthermore, the attempted resuscitation in this patient was complicated by the development of a pneumothorax during resuscitation efforts. This oft referred to case may have curtailed the use of antivenom in widow spider envenomation.

The etiology of allergic reactions following antivenom administration is unknown but most likely is the result of the foreign protein being introduced into the patient who has been previously sensitized to some component of the antivenom. The exact protein content of Black Widow Spider Antivenin (Merck) was not provided by the manufacturer.¹ The investigational Antivenin Latrodectus (Black Widow) (Analatro[®]) contains approximately 75 mg total protein per vial.²¹ As this is a F(ab)2 product rather than whole IgG, it would be anticipated the Merck product contains more total protein.

The low rate of adverse effects and no severe allergic reactions suggests that Black Widow Spider Antivenin[®] (Merck) appears to be safe when one vial was administered to both pediatric and adult patients.

Limitations

The major limitation is the retrospective use of poison control system data. The certified specialists in the poison information staff of the CPCS use a standardized data collection form and outcome criteria.²² The CPCS charts are coded as "related," "not related" or "unknown if related" to the drug. We only included charts coded as "related" in our analysis. However, there could be omissions from these records, and this data may not accurately reflect true events. Furthermore, clinicians are not mandated to report widow spider envenomation to the CPCS, and this could result in underreporting. Another limitation of our study is the small sample size of 96 cases. Similar to previous reports,^{11,12} our patients all described pain relief following the administration of the antivenom. However, we cannot exclude the potential contribution of the adjunctive therapies (e.g. opioids, benzodiazepines) in causing pain relief.

In addition, it is possible that more serious adverse reactions following antivenom administration actually occurred but were

not reported. All patients included in our study were either discharged from the ED or from the hospital. They were not followed up after discharge, therefore, we cannot exclude the development of delayed adverse reactions such as serum sickness; however, as stated previously, this would not be expected with only one vial being administered to all of our patients.

Conclusions

Our results suggest that Black Widow Spider Antivenin® (Merck) administration is relatively safe with mild to moderate adverse effects seen in only a small percentage of patients.

There were no deaths or severe allergic reactions identified. In addition, a single vial dose was sufficient to satisfactorily ameliorate patient symptoms. However, the extrapolation of retrospective poison center data must be interpreted cautiously. Further prospective studies are needed to corroborate our findings and elucidate the full safety profile on this antivenom and the incidence of adverse events.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the article.

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