



Safety of intravenous equine F(ab')₂: Insights following clinical trials involving 1534 recipients of scorpion antivenom

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ABSTRACT

Introduction: The technology of antivenom production has gradually changed since the earliest production of antisera around the turn of the 20th century. Use of early antisera was associated with frequent acute adverse reactions and serum sickness. New F(ab')₂ products, manufactured using pepsin degradation of immunoglobulin together with precipitation of unwanted protein and albumin serum fractions, should in concept cause fewer immune reactions in clinical use.

Methods: A linked set of five prospective clinical trials of an equine F(ab')₂ antivenom, together with one historical control study, were completed during development of the product for a Biological License Application through the US FDA. Adverse events were recorded and categorized, with particular attention to the frequency of immune reactions.

Results: A total of 1534 patients ages 0.1–90.5 years received antivenom, in Arizona and in Mexico, for treatment of scorpion envenomation. Total dosing ranged from 1 to 5 vials except for one outlier who received 10 vials. Estimated protein exposure was 12–275 mg per patient (outlier, up to 550 mg). Three patients (0.2%) had acute reactions to antivenom infusion (one urticaria, one urticaria and dyspnea, and one panic attack). Eight (0.5%) had rashes suggestive of Type 3 immune reactions, although none had the full syndrome of serum sickness. Two women were treated for envenomation during the first trimester of pregnancy, one of whom subsequently experienced a spontaneous abortion.

Conclusions: Rates of immune reaction to this product were two orders of magnitude lower than the range (up to 75% for early and 81% for late reactions) historically reported with use of minimally refined whole immunoglobulin products against a variety of infections and envenomations. Lower protein dose, greater purity of the active component, lack of the immunogenic Fc portion of the immunoglobulin molecule, and slow intravenous infusion are likely to be the reason for this. Clinical implications of a safer product include that it can be employed in settings where antivenom was once considered too dangerous to use, such as primary care clinics and remote rural areas.

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1. Introduction

“Antivenom,” in the most general sense, describes a family of products that are produced from the blood of hyperimmunized animals for the purpose of treating adverse effects of venom in humans.

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“Antiserum” against venom, sometimes referred to as “first generation antivenom,” was brought to its first commercial success by Albert Calmette, whose work with the Pasteur Institute from the 1880's through the early 20th century resulted in international distribution of the first blood product widely claimed to be effective against snakebite (Calmette, 1895, 1896, 1908). This product, like antitoxins for treatment of tetanus and diphtheria, was made by serially immunizing horses with increasing doses of antigen, until serum collected from the horses was capable of neutralizing the effects of the immunogenic toxin in laboratory animals. Antisera of this kind may be unrefined except for removal of red blood cells, or they may be minimally purified beyond that stage. Their use is associated with acute and delayed adverse reactions, sometimes fatal (Thresh, 1901; Currie, 1907; Heller and IM, 1908; Gaines, 1908; Wiley, 1908; Lucas and Gay, 1909). In fact, use of diphtheria antitoxin at the turn of the 20th century led to awareness that humans may become sensitized to antisera after first administration, and that with each additional dose given the likelihood of adverse reactions may increase (Currie, 1907; Lucas and Gay, 1909). Individuals with horse allergy or ‘horse asthma’ appeared to be more likely to develop an immediate reaction upon first administration of a horse serum-derived antitoxin (Heller and IM, 1908; Goodale, 1914).

During the course of the 20th century, improvements were made in the separation of serum or plasma into component parts, such that “immunoglobulin therapy” began to replace “serotherapy” of toxin-induced diseases. In particular, techniques were developed for removal of albumin, and of varying amounts of serum globulins, by “salting out” or precipitating unwanted components with ammonium sulfate or caprylic acid (Rojas et al., 1994) while holding back the immunoglobulin fraction for subsequent pharmaceutical production. The resulting “second generation antivenoms” ideally contain an enriched proportion of immunoglobulin, with consequently increased per-mg potency and fewer immune reactions, although in practice the purity of the final product may not be sufficient for this effect to be realized (Corrigan et al., 1976; Sullivan et al., 1995, 1999; Otero et al., 1999). While the safety profile of recent antivenoms has in some cases improved compared to that of the earliest antisera (Thiansookon and Rojnuckarin, 2008), their use continues to result in serious reactions worldwide. In Sri Lanka and India, 43–81% of antivenom recipients have acute adverse reactions (deSilva et al., 2011). Antivenoms used in the United States have been associated with acute reactions in 1–38% and delayed serum sickness in 50–75% of recipients (Corrigan et al., 1976; Tanen et al., 2001; LoVecchio et al., 1999, 2001, 2003; LoVecchio and McBride, 2003). Greater purity of immunoglobulin has been reported following caprylic acid fractionation than that historically reported following ammonium sulfate fractionation, but whole immunoglobulin antivenom purified with caprylic acid still carries a risk of acute and delayed serum reactions, with early acute reactions in 11–25.6% of snakebite patients who receive it (Otero-Patiño et al., 1998, 2012; Otero et al., 1999; Abubakar et al., 2010) and delayed reactions in 5.3–10.8% (Abubakar et al., 2010).

In the latter half of the 20th century, enzymatic degradation of immunoglobulin via pepsin (Parfentjev, 1936,

1938, 1939; Hansen, 1938; Pope, 1939) or papain (Porter, 1959) came into use in antivenom production. Cleavage of immunoglobulin and isolation of the resulting Fab or F(ab')₂ fragments, combined with a “salting out” step and/or with affinity column purification, led to the acceptance of “third generation antivenoms” or “fabotherapeutics” (Alagón, 2002) throughout much of the world. In theory, these products should be more potent (per mg of protein) and safer to use than their whole-immunoglobulin predecessors, particularly in cases where the purification of the Fab or F(ab')₂ molecule is relatively complete. Clinical reports show a range of safety profiles, with early reactions ranging from 0 to 37% and delayed serum sickness from 0 to 19% (Otero-Patiño et al., 1998, 2007; Dart et al., 1997; Schaeffer et al., 2012; Chippaux et al., 2007).

Today, antivenoms representing the full spectrum from crude serotherapy to refined fabotherapy are in use around the world. The risk of morbidity or mortality from antivenom itself varies widely, with great public health implications (Isbister et al., 2008; Natu et al., 2006). In particular, more refined products may be safe enough for routine use in geographically remote clinics, while less refined products may carry a great enough risk of anaphylaxis to prohibit such use, effectively limiting access of essential emergency treatment. Better safety data are needed for all antivenoms, so that policy makers can balance risks and benefits of supply strategies, and so that physicians can make better-informed decisions regarding the urgency and severity threshold for envenomation treatment.

We present here prospectively-collected safety information, during the course of formal clinical trials in the United States, involving 2-week follow-up of more than 1500 patients treated with an antiscorpion F(ab')₂ antivenom.

2. Methods

2.1. Patients and protocols

Between 2004 and 2011, formal clinical trials were conducted in Arizona and in Mexico under a US Investigational New Drug Application for scorpion antivenom. A total of 1534 children and adults envenomated by *Centruroides* scorpions received antivenom, through 5 related protocols, during this time. Table 1 lists these studies and provides detail on demographics and treatment numbers.

The results of the pivotal double-blind, placebo controlled clinical trial have been published (Boyer et al., 2009). In this study, 8 patients received antivenom and 7 received placebo in the pediatric ICU setting.

The results of two open-label pediatric protocols, essentially identical except that one was performed in Mexico and the other in Arizona, are pending publication at this time (Boyer et al., 2013). In these 2 studies a total of 78 children (plus one adult enrolled in violation of inclusion/exclusion criteria) received antivenom; historical controls for these studies were obtained from chart review of 97 cases in Arizona pediatric ICUs.

A separate open-label protocol in Mexico involved the treatment of symptomatic adults. A total of 22 patients received antivenom under this protocol.

Table 1

Studies included, demographics and antivenom (protein) exposure.

Protocol design	Treatment doses	N by treatment	Protein exposure (range)	Age range in years (mean)	Sex (% M, F)	% M/F (Black/White/Hispanic/Other)
Double-blind, randomized, placebo-controlled trial	3 vials	Antivenom: 8 Placebo: 7	36–165 mg 0 mg	1–6 (2.0) 1–10 (3.0)	4 M, 4 F (50, 50) 3 M, 4 F (42, 58)	3 W, 3 H, 1 O 1 B, 4 W, 1 H, 1 O
Arizona Children						
Open-label trial	2–4 vials	22	24–220 mg	19–55 (33)	8 M, 14 F (36, 64)	22 H
Mexico Adults						
Open-label trial	3–10 vials	29	36–550 mg	0.9–9 (3.0)	16 M, 13 F (55, 45)	29 H
Mexico Children						
Open-label trial	3–4 vials	49	36–220 mg	0.6–51 (4.3)	30 M, 19 F (61, 39)	0 B, 9 W, 5 H, 35 O
Arizona Children ^a						
Treatment protocol	1–5 vials	1425	12–275 mg	0.03–90.5 (14.8)	744 M, 681 F (52, 48)	32 B, 797 W, 393 H, 203 O
Arizona All ages						
Historical controls	none	97	0 mg	1–16 (3.9)	52 M, 45 F (54, 46)	0 B, 32 W, 9 H, 6 O 50 unknown
Arizona Children						
Overall Antivenom groups	1–10 vials	1534	12–550 mg	0.1–90.5	802 M, 732 F (52, 48)	B, W, H, O
Overall controls	0 vials	104	0 mg	1–16	55 M, 49 F (53, 47)	1 B, 36 W, 10 H, 7 O, 50 unknown

^a One adult was enrolled in violation of the Arizona open-label pediatric protocol; this individual is excluded from demographic calculations here but is included in the safety analysis for adverse events.

A multicenter treatment protocol, at 27 sites in Arizona, enabled the use of antivenom in patients of all ages between the time when more formal trials were completed and submission of the Biological License Application. A total of 1425 children and adults received antivenom under the multicenter treatment protocol before close of data collection for this analysis.

In all protocols, prior medication was allowable under inclusion/exclusion criteria. Inclusion criteria included “medically important systemic signs of scorpion envenomation,” corresponding to either Grade 3 or Grade 4 on the severity score used in Arizona (Curry et al., 1983–1984; Boyer et al., 2009). In all prospective protocols, 1–3 vials of antivenom were diluted in 50 ml saline and infused intravenous over a minimum of 10 min. All subjects, except for historical controls, were prospectively monitored for adverse events during the initial treatment period, and acute reactions were recorded. Follow-up was performed by telephone to determine signs of serum sickness, as well as ongoing envenomation effects and/or other adverse events. Patients were referred for clinic evaluation as indicated. In most protocols, subjects were contacted 7 days and 14 days post-discharge; those in the treatment protocol were contacted 24 h and 14 days after hospital discharge. Retrospective controls could not be contacted for follow up, thus adverse events for these cases reflect only the hospitalization period. Adverse events were recorded and categorized according to severity and apparent cause using the most current version of the Medical Dictionary for Regulatory Activities (MedDRA). A research coordinator reviewed all adverse events for consistency of coding among sites. Serious adverse events, and events suggestive of acute hypersensitivity (e.g., rash or respiratory distress during or immediately following antivenom infusion) or of serum

sickness (e.g., urticaria, rash, arthralgia, myalgia, or fever 5–15 days after treatment) were secondarily reviewed by the central principal investigator, whose clinical judgment as to presence or absence of immune reaction was recorded.

All protocols were reviewed and approved by the applicable Institutional Review Boards (IRBs). Patients or parents provided informed consent in all prospective protocols, and the historical controls study was exempted from the requirement for consent following review by the IRB. Studies were registered on Clinicaltrials.org (registry numbers NCT 00696683, NCT01599936, NCT01599923, NCT00624078, NCT00685230).

2.2. Investigational drug

Except for the 7 placebo recipients and 97 historical controls, all patients received Centruroides (scorpion) immune F(ab')₂ (equine) injection manufactured by Instituto Bioclon, SA de CV (Mexico). In the USA, studies were conducted under an Investigational New Drug Application, and the product was subsequently given marketing approval under the trade name Anascorp.

According to the US package insert, “Anascorp [Centruroides (Scorpion) Immune F(ab')₂ (Equine) Injection] is a sterile, nonpyrogenic, lyophilized, polyvalent preparation of equine immune globulin F(ab')₂ fragments, manufactured from plasma of horses immunized with venom of *C. noxi*, *C. l. limpidus*, *C. l. tecomanus*, and *C. s. suffusus*. The product is obtained by pepsin digestion of horse plasma to remove the F_c portion of immune globulin, followed by fractionation and purification steps. The F(ab')₂ content is not less than 85%, Fab' content is not more than 7%, and the product contains less than 5% intact immunoglobulin. Each vial of Anascorp contains 45–80 mg of sodium

chloride, 4.3–38.3 mg of sucrose, and 6.6–94.9 mg of glycine as stabilizers. Trace amounts of pepsin, cresol (<0.41 mg/vial), borates (<1 mg/vial), and sulfates (<1.7 mg/vial) may be present from the manufacturing process. Each vial contains no more than 120 mg of protein and will neutralize at least 150 LD₅₀ of *Centruroides* scorpion venom in a mouse neutralization assay.” Assays of lots used for the studies in this report contained between 12 and 55 mg of lyophilized protein per vial. Protein concentration, percentages of Fab’ and F(ab’)₂, and IgG content were determined by the Bradford method, size exclusion chromatography and SDS-PAGE, respectively. All procedures and standards were validated following FDA regulations.

3. Results

Table 1 details case enrollment in each study protocol, with demographics and total drug exposure in terms of vials of antivenom and estimated total protein dose. In all, 330 adults (including 2 pregnant women and 77 patients over the age of 65) and 1204 children under age 18 received antivenom. Pediatric and adult dosing were the same (1–5 vials except for one outlier). Protein dose was estimated based on a range of protein per vial of 12–55 mg; using extremes this means that typical cases received between 12 and 275 mg protein, and the pediatric outlier who received 10 vials had a protein dose of between 120 and 550 mg protein. Across all prospective protocols, 96% of patients remained in contact through the follow-up period.

Table 2 details the number of antivenom recipients and controls who experienced any adverse event (AE) regardless of cause, any serious adverse event (SAE) regardless of cause, acute hypersensitivity consistent with drug reaction, probable Type 3 (delayed) immune reaction to the antivenom, and common AEs not specific to antivenom use. Adverse events in the historical controls population most likely represent an underestimate, both because of the retrospective design and because only the

hospitalization period was included, vs two weeks follow-up in the other groups. Despite this, the control group showed more AEs than antivenom recipients overall, particularly in categories reflecting serious illness (intubation, hypoxia, aspiration pneumonia, stridor). Common sequelae of early envenomation (vomiting, pyrexia) were comparable between groups, with if anything a higher rate among controls.

Younger patients (up to 5 years of age) were more likely to be affected severely by the envenomation, so it is not surprising they had the highest incidences of vomiting, pyrexia, rash, rhinorrhea, respiratory distress, and aspiration. AEs that were reported more frequently by older patients included subjective complaints such as fatigue, pruritus, headache, nausea, and musculoskeletal/peripheral nerve symptoms (e.g., arthralgia, myalgia, hypesthesia, stiffness, pain). Patients weighing 10 kg or less had the highest overall incidence of AEs. Female patients had a higher incidence of AEs than males.

Of the two pregnant patients, one was a 23-year-old woman who presented unaware of her early first-trimester pregnancy. She had aberrant eye movements, tongue fasciculations, paresthesias and chest heaviness, all of which had resolved 2 h after receiving 3 vials of antivenom. Pregnancy was confirmed one week later, followed shortly thereafter by spontaneous miscarriage. The second case was a 28-year-old who presented at 8 weeks’ gestation, also with aberrant eye movements, tongue fasciculations and paresthesias. Her symptoms resolved 70 min after receiving 4 vials of antivenom; and she later delivered a healthy full-term 9-lb baby boy.

Of 421 patients with adverse events, only 4 (<1%) were judged “definitely related to study drug” by investigators. These were two cases of intravenous line infiltration (both resolved with replacement of the line), one case with erythema and edema at the IV site (resolved spontaneously), and one case of severe rash in the groin and underarm areas, beginning 9 days after treatment and diagnosed as serum sickness by the evaluating physician.

Table 2
Adverse events (serious, immunological or affecting at least 2% of treated cases or controls).

N	Antivenom number (%)	Historical control number (%)	Placebo number (%)
	1534 (100)	97 (100)	7 (100)
Patients with at least one AE	421 (27)	38 (39)	1 (14)
Patients with at least one treatment-emergent SAE	34 (2.2)	0 (0.0)	0 (0.0)
Patient deaths	0 (0.0)	0 (0.0)	0 (0.0)
Type 1 hypersensitivity reaction	3 (0.2)	NA	0 (0.0)
Type 3 immune reaction	8 (0.5)	NA	0 (0.0)
Vomiting	72 (4.7)	7 (7.2)	0 (0.0)
Pyrexia	63 (4.1)	6 (6.2)	1 (14)
Rash	41 (2.7)	1 (1.0)	1 (14)
Nausea	32 (2.1)	0 (0.0)	0 (0.0)
Pruritus	31 (2.0)	0 (0.0)	0 (0.0)
Intubation	2 (0.1)	5 (5.2)	0 (0.0)
Hypoxia	1 (0.1)	4 (4.1)	0 (0.0)
Pneumonia aspiration	3 (0.2)	4 (4.1)	0 (0.0)
Stridor	2 (0.1)	3 (3.1)	0 (0.0)
Hallucination	0 (0.0)	2 (2.1)	0 (0.0)
Blood potassium decreased	0 (0.0)	2 (2.1)	0 (0.0)
Lumbar puncture	0 (0.0)	2 (2.1)	0 (0.0)
Fell out of hospital crib or bed	0 (0.0)	2 (2.1)	0 (0.0)

Concomitant medications were permitted in all protocols. The most commonly used were benzodiazepines (37%), opiates (25%), analgesic-antipyretics (24%), and antihistamines (20%). Somnolence and nausea/vomiting were more commonly reported in recipients of benzodiazepines and opiates than in other patients.

3.1. Acute reactions

Prior history of antivenom use, and/or of scorpion sting, was recorded in prospective studies other than the multicenter treatment protocol. In all, 14 of 108 antivenom recipients in these studies (13%, 9 adults and 5 children) reported being stung previously, and of these 5 (5%, 4 adults and 1 child) had received equine antivenom. None of these had acute reactions at the time of drug infusion; however, one subject in the treatment protocol, who had received equine antivenom for 2 prior stings (described following), had an apparent Type 1 hypersensitivity response during the study.

Three patients (0.2% of antivenom recipients) were identified as having a possible acute hypersensitivity reaction. The first was a 3.8-year-old male with a history of peanut allergy, who received 3 vials of antivenom in 50 ml saline, over 20 min time, 2.4 h after a scorpion sting. Five minutes after the infusion ended, he developed urticaria, emesis and labored breathing. These resolved after treatment with diphenhydramine, solumedrol, and epinephrine. Case review revealed that a nurse involved in his care had eaten a peanut butter sandwich between setting up and taking down the infusion. Later skin prick testing showed cutaneous reactivity to horse serum and to peanuts. Diagnosis was Type 1 hypersensitivity, but it was not possible to distinguish whether this was because of antivenom or peanuts.

The second was a 6-year-old male who was stung on the shoulder by a scorpion 3 h before treatment. His past medical history was noteworthy for two prior scorpion stings, for which he had received the same investigational equine antivenom 3 months and 6 months before this event. Prior to the patient being seen at the hospital, his father administered epinephrine in an apparent misunderstanding that scorpion stings were “allergic”. He presented with typical neuromotor toxicity. He received 3 vials of antivenom in 50 ml saline intravenous over 11 min. At the end of the infusion, the child complained of pain at the back of his neck. Urticaria was observed, progressing to involve all four extremities and the trunk over the next 15 min. This resolved one hour after treatment with IV diphenhydramine, IV corticosteroids, and famotidine. Although it was possible that the urticaria represented an allergy to scorpion venom, which might have been transiently suppressed by prehospital epinephrine, investigators judged that this was more likely a Type 1 hypersensitivity reaction to the antivenom.

The third case was a 27-year-old woman who was stung on the right thigh by a scorpion 2 h before treatment. Her past medical history was noteworthy for panic attacks. She presented with abnormal eye movements and tongue fasciculations. An intravenous infusion of 3 vials of antivenom was initiated, but after 1–2 min the patient complained of

facial flushing and shortness of breath. The infusion was stopped and IV diphenhydramine was administered. Within 2 min the patient reported she felt back to normal and the infusion was resumed. An hour after the initial infusion, the patient remained symptomatic, so another vial of antivenom was administered, without further difficulties. Additional medications during care included lorazepam, methylprednisolone and tetanus vaccine. She was discharged after another hour of observation, and remained asymptomatic during the 2-week follow-up period. Investigators judged that this adverse event was likely a panic reaction; but Type 1 hypersensitivity could not be ruled out.

3.2. Serum sickness

A total of 13 patients out of 1534 (0.8%) were identified, either by investigator judgment or by systematic database review, as having rashes, myalgias, arthralgias, or fever with timing suggestive of possible serum sickness. Of these, none had the full serum sickness syndrome. The most severe of these had been evaluated clinically for probable serum sickness, based on timing and a typical cutaneous reaction, and this case has been reported previously (Jackson and Curry, 2008). Five were recognized on review as symptomatic secondary to a bone fracture, a bubble bath allergy, or intercurrent viral illness, leaving a total of 8 (0.5%) for which Type 3 immune reaction was judged the best explanation for clinical findings. Of these, 2 received no treatment, 3 were treated with over-the-counter hydrocortisone cream or antihistamine, and 3 received oral corticosteroids. No recipient of prior antivenom developed signs of Type 3 immune reaction.

3.3. Serious adverse events

Investigators identified 41 cases as having SAEs. Of these, 34 were treatment-emergent (starting after use of antivenom). Most SAEs were not related to antivenom treatment; many were caused by vomiting and aspiration or by oversedation. Three were judged “possibly related to treatment”: these included one child with rash and stridor (described previously); one 4-year-old child who was endotracheally intubated because of possible aspiration while vomiting, but for whom acute reaction could not be fully ruled out because the event occurred shortly after antivenom administration; and one 62-year-old woman with a history of pancreatitis who had a rising lipase level during the period of study observation.

4. Discussion

In much of the world, use of antivenom is restricted to monitored hospital units where resuscitative equipment is readily available in the event of an acute reaction. Transfer of patients from remote areas lacking such facilities results in delays to definitive care and increased costs and hardship for patients. Once in a well-equipped facility, weighing the risks and benefits of antivenom administration can complicate medical decision-making, further delaying definitive treatment. However, in this series of 1534 prospectively monitored antivenom recipients, acute reactions

attributable to antivenom were rare, occurring in at most 3 patients (0.2%), fewer if the alternative etiologies of panic attack and peanut allergy are considered in 2 of 3 cases. This safety record, two orders of magnitude better than what was once expected with minimally-refined serum preparations, suggests that previous practice may in some circumstances be modified, to encourage early use of antivenom at primary care facilities. This finding agrees with previous informal reports from clinicians in rural Mexico, where scorpion antivenom has apparently been used safely since the advent of fabootherapeutics, and with reports of experience with snake antivenom produced by the same manufacturer (Boyer, 2010; Chippaux et al., 2007). This contrasts, however, with findings using pepsin-digested, ammonium sulfate precipitated antivenoms from a different source, to treat snakebite (Otero-Patiño et al., 1998), and until factors responsible for the difference have been better studied care must be taken not to over-generalize the results.

These clinical trials were not designed to prove why the early adverse event rate was so low, but several contributing factors should be considered. First, our patients received an unusually low total dose of foreign protein, ranging approximately from 12 to 275 mg. This is lower than historical antivenom dosing, in part because scorpion envenomation requires less immunoglobulin to neutralize than does snakebite, but also because the potency of the specific product was high on a per-mg basis, reflecting a high proportion of active principle in the protein mixture. Second, the $F(ab')_2$ immunoglobulin derivative used in this product lacks the immunogenic Fc portion that interacts with complement. Third, purification steps required to support licensure under the US FDA may also have reduced the presence of particulate and chemical contaminants that may contribute to adverse reactions. Fourth, it has been suggested that scorpion envenomation itself may protect against early adverse reactions, because of transient catecholamine release following venom exposure (Abroug et al., 2003; Amaral et al., 1994; Noura et al., 2005; Trejo et al., 2012). Finally, all patients received dilute antivenom, in 50 ml saline, which was infused over no less than 10 min time, thereby minimizing the impact of concentration or rate-dependent early reactions.

The rate of delayed reactions observed in this series of studies – 8/1534 or 0.5% – was also two orders of magnitude lower than what was once expected (61% following treatment for scorpion sting and 50–75% following snakebite), when the term “antivenom” referred to minimally-refined whole-IgG serum preparations. Considering that these reactions resolved either spontaneously or after outpatient use of antihistamines or steroids, the risk of clinically significant serum sickness from use of this product, at these doses, appears almost negligible. Factors involved may have included lower dose of foreign protein, greater product purity, lower immunogenicity and faster clearance of $F(ab')_2$ than whole immunoglobulin.

Although the methodology of the historical control study precluded precise comparison with prospective safety results, it is interesting to consider the nature of the nonspecific adverse events reported with and without antivenom treatment. Despite the limitations of retrospective review,

which include a brief record and lack of mandatory AE documentation, this group had what appeared to be a higher rate of AEs overall, particularly those attributable to critical illness and intensive care. This is not surprising, given that very few antivenom recipients required hospital admission, and it is most likely a reflection of the effectiveness of the antivenom, consistent with observations at a referral center that did not, at first, participate in the antivenom studies (O'Connor and Ruha, 2012). Future studies of treatment outcomes, public health, and pharmacoeconomics should take into consideration this apparent difference.

Limitations of the study include the lack of a large prospective control group and the potential for suppression of some adverse reactions by concomitant administration of antihistamines, which affected 20% of cases. Antihistamines were in many cases given at the outset of care, perhaps in the mistaken belief that scorpion envenomation was an “insect bite” of allergic nature; they were also administered for rashes and upper respiratory symptoms attributable to common childhood conditions during follow-up, thus the rate of antihistamine use in cases with such symptoms was somewhat higher, overall.

In summary, this study supports the expectation that at least some “fabootherapeutic” agents may now be made safe enough for routine use in the relatively remote clinic settings where snakebite and scorpion sting are most dangerous. For this particular scorpion antivenom, administered dilute over 10 min time, acute adverse reactions affect up to one in 500 cases and are manageable using established emergency care. Delayed reactions affect one in 200 patients and are so mild as not to meet the syndromic definition of “serum sickness” at all.

Ethical statement

The manuscript accompanying this submission is original work by the authors and by others named in the acknowledgments. The safety issues analyzed in detail here were briefly mentioned in prior manuscripts describing the clinical efficacy of the antivenom, and this topic was the subject of a platform presentation at Venom Week 2012, in Honolulu; but this analysis has not previously been submitted or published. All clinical research was approved by the applicable Institutional Review Boards, and informed consent was obtained for all prospectively-enrolled patients. All funding sources and potential conflicts of interest have been disclosed.

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designed the studies, collected and analyzed the data, wrote the manuscript, and vouch for the accuracy and completeness of the reported analyses. We are grateful to Judi Carrington for her invaluable support in administrative management of the team, to Lisbeth Gaf for wise counsel, and to Sarah Graziani, without whom the project would never have happened at all.

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Conflict of interest

Dr. Alagón reports that, at the time of the study, his laboratory was partially funded by and he provided consulting services to Instituto Bioclon SA de CV; Dr. Ruha reports having provided consulting services to Rare Disease Therapeutics; and Dr. Boyer reports that she received grant funding from Instituto Bioclon SA de CV and from Rare Disease Therapeutics Inc. Ms. Degan, Dr. Mangin, and Ms. Mallie report no conflicts.

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