INCIDENCE OF SERUM SICKNESS AFTER THE ADMINISTRATION OF AUSTRALIAN SNAKE ANTIVENOM (ASP-22)

ABSTRACT

Context: Serum sickness is a delayed immune reaction resulting from the injection of foreign protein or serum. Antivenom is known to cause serum sickness but the incidence and characteristics are poorly defined.

Objective: To investigate the incidence and clinical features of serum sickness following the administration of Australian snake antivenoms.

Materials and Methods: This was a prospective cohort study of patients recruited to the Australian Snakebite Project who received snake antivenom from November 2012 to March 2014. Demographics, clinical information, laboratory tests and antivenom treatment were recorded prospectively. Patients administered antivenom were followed up at 7-10 days and 6 weeks post-antivenom. The primary outcome was the proportion with serum sickness, pre-defined as three or more of: fever, erythematous rash/urticaria, myalgia/arthralgia, headache, malaise, nausea/vomiting 5-20 days post-antivenom.

Results: During the 16 month period, 138 patients received antivenom. 23 were not followed up (unable to contact, tourist, child, bee sting) and six died in hospital. Of 109 patients followed up, the commonest reason for antivenom was venom induced consumption coagulopathy in 77 patients. An acute systemic hypersensitivity

reaction occurred post-antivenom in 25 (23%) and eight (7%) were severe with hypotension. Serum sickness occurred in 32/109 (29%) patients, including 15/37 (41%) given tiger snake, 6/15 (40%) given polyvalent and 4/23 (17%) given brown snake antivenom. There was no association between the volume of antivenom and serum sickness, p=0.18. The commonest effects were lethargy, headache, muscle/joint aches and fever.

Discussion: The incidence of serum sickness after snake antivenom in Australia was higher than earlier investigations which failed to define symptoms or follow up patients, but similar to more recent studies of antivenoms in the United States.

Conclusion: Serum sickness is common with Australian snake antivenom but does not appear to be predictable based on the volume of antivenom administered.

INTRODUCTION

Snake envenoming is a major public health issue worldwide, with significant morbidity and mortality in the rural tropics. [1] Although antivenom is the main treatment for snake envenoming, adverse effects from antivenom continue to be a major problem in many countries. [2-5] Antivenom is an animal serum–derived pharmaceutical and when injected into humans can produce severe adverse reactions, including anaphylaxis and death. [6, 7] The focus of most studies has been immediate-type reactions to antivenom, including anaphylaxis, because they can be severe and life-threatening and occur within 24h of intravenous administration of snake antivenom. They have been reported to occur in as high as 88% [8] or as low as 3% [9] of patients given antivenom. Such high variability reflects the heterogeneity in the safety profile of these products. [10] The other important adverse effect after antivenom is serum sickness, which is a delayed immune reaction and occurs days after antivenom administration. It is poorly defined in terms of incidence, clinical features and potential treatments.

Serum sickness was first described in the early 1900s at the same time as anaphylaxis and allergy were first being described. [11, 12] The first pathophysiological description and initial characterisation of serum sickness was made by Clemens von Pirquet and Bela Schick in 1905. [13, 14] It was based on clinical observations of the reactions to the administration of large amounts of foreign proteins, such as antitoxins given for diphtheria and tetanus. [14] Pirquet described how these disease symptoms were not

terminated by the immune response but were actually initiated by the host immune response; he described the newly formed antibodies reacting with antigen and forming toxic bodies – now recognised as immune complexes which fix complement. [14] With the change to active immunisation and the use of humanised or recombinant antibodies, serum sickness is now rarely seen except after the administration of antivenoms, which are all foreign animal-derived protein. Serum sickness after antivenom has a delayed onset between 5 and 14 days after administration, when the immune system mounts an IgG-mediated antibody response. [7, 10] Clinically this manifests with rash, fever, arthralgia, myalgia, headache and gastrointestinal symptoms. In one study of whole IgG antivenom, the incidence of late reactions increased with the total amount of heterologous protein administered. [15]

The incidence and characteristics of serum sickness following the administration of antivenoms is poorly defined, mostly because patients uncommonly return to health centres after discharge. [10, 15-17] The objective of this study was to investigate the frequency and clinical features of serum sickness following the administration of Australian snake antivenoms in envenomed patients.

METHODS

This was a prospective cohort study of patients recruited to the Australian Snakebite Project who received snake antivenom from 21st November 2012 to March 2014 and were followed up for 6 weeks after their admission to hospital. The Australian snakebite project is an ongoing, multicentre prospective observational study that

recruits patients with suspected snakebite or snake envenoming from over 100 hospitals throughout Australia. The design of the Australian snakebite project has been previously described in detail, [18-21] and approval has been obtained from over 18 human research ethics committees throughout Australia, including the Northern Territory Department of Health and Menzies School of Health Research, Human Research Ethics Committee No: HR-03-802. Informed written consent was obtained from all participants in this study.

Demographics, clinical information, laboratory tests, antivenom and other treatments, adverse reactions to antivenom and complications are recorded prospectively on clinical research forms by the treating health care workers for all patients recruited to the Australian snakebite project. The research forms are faxed to the investigators and this information is then entered into a purpose-built relational database (Microsoft Access) by trained research staff. For this study of serum sickness any patient who received antivenom was followed-up by telephone 7 to 10 days and 6 weeks after administration of the antivenom by a single research assistant (RTK). The calls were recorded on a dedicated datasheet and then transferred to the database (described above). The definition of serum sickness and outcomes of the study were defined prior to patients being prospectively followed up.

For the analysis, data was extracted from the Australian snakebite project database from November 2012 to March 2014, and included age, sex, bite date, antivenom

type and dose, immediate antivenom reactions and symptoms of serum sickness. The following symptoms were recorded on the follow up datasheet: headache, muscle/joint aches (myalgia/arthralgia), fever/chills, malaise, nausea or vomiting, rash/urticaria, lethargy, diaphoresis, abdominal pain and any other symptom comments. In addition, any treatments the patient had been given after discharge were recorded, specifically asking about the use of corticosteroids.

The primary outcome was the proportion of patients with serum sickness which was pre-defined as three or more of the following clinical features 5 to 20 days after antivenom administration - fever, erythematous rash/urticaria, myalgia/arthralgia, headache, malaise and nausea/vomiting.

To help clarify the clinical features of serum sickness, previous studies on the characterisation and incidence of serum sickness from snake antivenom were also reviewed. This was done through an English-literature search of PubMed, Medline and Google Scholar using the terms 'serum sickness', 'late reactions' or 'late adverse reactions' with 'antivenom' or 'snake antivenom'.

For descriptive statistics, percent frequency, median and interquartile ranges (IQRs) for non-parametric data were used. The continuous variable of antivenom volume for patients with and without serum sickness were compared graphically and with the Mann-Whitney test for non-parametric data. Contingency tables with Fisher's exact test or Chi square test were used to compare categorical outcomes for patients with and without serum sickness. We also conducted a sensitivity analysis where all

patients (including those lost to follow up) were included and assumed to not have serum sickness, this calculation is the lowest possible frequency of serum sickness that could occur. All analyses and graphics were done in GraphPad Prism version 6 for Windows, GraphPad Software, San Diego California USA, www.graphpad.com.

RESULTS

There were 279 patients recruited to the Australian snakebite project during the 16 month study period, but only 138 received antivenom - 112 were not envenomed and 29 were envenomed but did not receive antivenom (e.g. red-bellied black snake envenoming which is not always treated with antivenom, and delayed presentations); total excluded 141. Of these 138 cases, 21 could not be contacted or followed up (no answer, no contact details, tourist), one was a bee sting and not followed up and one was a child (<5 years old), six died in hospital, (Figure 1). One hundred and nine patients (82 males) with a median age of 44 years (IQR: 26 to 56 years; Range: 8 to 88years) were followed-up for serum sickness, (Table 1).

The most common reason for antivenom administration was venom induced consumption coagulopathy (VICC) in 77 patients. An acute systemic hypersensitivity reaction occurred in the first hour after antivenom in 25 of the 109 (23%) and eight (7%) were severe anaphylaxis with hypotension (Table 1). The most commonly used antivenoms were tiger snake (34%), brown snake (21%), brown+tiger snake (17%), and polyvalent (14%) in patients followed-up, (Table 2).

Serum sickness occurred in 32 of the 109 patients (29%) and was most common for tiger snake antivenom, (3000 units) in 15/37 (41%) patients followed by polyvalent antivenom, (40000 units) in 6/15 (40%) patients and least likely for brown snake antivenom, (1000 units) in 4/23 (17%), (Table 2). The lowest possible frequency of serum sickness for this study was 32 out of 130 patients (25%) assuming all patients not followed up did not have serum sickness. Eight of the 109 patients (7%) were aged below 16 years and two of these developed serum sickness (one to tiger snake antivenom, 3000 units and one to black snake antivenom, 18000 units). A visual breakdown of the proportion of patients with serum sickness for each age range is given in Figure 2.

There were too few cases to look for an association between antivenom type and presence of serum sickness using a Chi square test. There was no association between the volume administered and serum sickness, (Mann Whitney test, p=0.18, Table 2 and Figure 3). 5/32 (16%) patients with serum sickness had an acute reaction compared to 20/77 (26%) patients with no serum sickness having an acute reaction, p = 0.32. The most common symptoms found in patients with serum sickness were lethargy (94%), headache (91%), muscle/joint aches (72%), fever or chills (56%), diaphoresis (44%), malaise (41%), and nausea or vomiting (34%) while only 28% of patients had abdominal pain and 19% had a rash, (Table 3). All of these symptoms were more common in patients with serum sickness compared to those without, although lethargy, headache and muscle/joint aches did occur in >10% of all patients,

(Table 3). Five patients had two primary symptoms, four had myalgia and one other symptom, however these cases did not meet the diagnostic criteria for serum sickness. Five patients were treated with corticosteroids by their general practitioner for serum sickness.

DISCUSSION

This study found that serum sickness occurred in slightly more than one-quarter (29%) of patients after the administration of Australian snake antivenom. Serum sickness was most common (41%) with tiger snake and polyvalent antivenoms (40%), and least common (17%) with brown snake, but this study was too small for a statistical comparison. There was no statistical association between the volume of antivenom administered and the occurrence of serum sickness. There was also no relationship between immediate hypersensitivity reactions and serum sickness and this result is similar to Lavonas et al. [22] who also found no association between the proportions of immediate hypersensitivity reactions and serum sickness.

A review of the literature found that the incidence of serum sickness from snake antivenom varies considerably across geographical locations and snake antivenom types (range: 5 to 56%) [15, 22-28] (Table 4). The design of these studies and the range of symptoms used to identify serum sickness differed between studies and in some cases were quite unclear, especially in earlier investigations [27, 28] making this incidence data difficult to compare. Furthermore, it is likely that the immunological events causing "serum sickness" vary significantly in intensity, with a broad

spectrum of symptom severity. Thus, a patient with mild arthralgia may not satisfy diagnostic criteria but could represent a mild form of immune reaction. This appeared to be the case in our study where four patients had myalgia and one other symptom (most commonly headache), which did not meet the diagnostic criteria, but was likely to be a mild form of serum sickness. This suggests that there is a spectrum of serum sickness, like most other hypersensitivity diseases, making diagnostic criteria somewhat artificial. In contrast, diagnostic criteria are useful from a research perspective and future studies will need to refine the criteria for serum sickness.

In early investigations, Trinca, [28] found that in 100 patients that received antivenom, only six (7%) developed serum sickness; but the symptoms were not detailed and no cases were followed up. In another early investigation of 28 patients treated with snake antivenom from Port Moresby General Hospital, 7% were reported as having serum sickness. [27] Again, no associated symptoms were reported. In five more recent studies from the United States the incidence of serum sickness was found to range from 5% to 23% when using defined, yet variable symptom criteria (Table 4). [22-26] In a sixth United States study, LoVecchio et al, [15] identified 56% of patients as having serum sickness based on the three symptoms of fever, arthralgia and pruritus (Table 4). In the patients investigated in our study, lethargy, headache, muscle/joint aches and fever or chills were the most common symptoms, and diaphoresis, malaise, nausea or vomiting, abdominal pain and rash were less common. Future

studies will need to improve and standardise the diagnostic criteria for serum sickness, remembering that the original description by Pirquet and Schick included fever, rash, kidney injury with proteinuria, lymphadenopathy and joint symptoms, [14] and that there should be correlation between symptoms and IgG/immunocomplexes levels in serum and urine. [13]

In delayed antivenom reactions, the immune system of the patient receiving the antivenom recognises the heterologous proteins as foreign and mounts an IgG-based antibody response towards them via the classical pathway, as well as activating neutrophils. This manifests clinically as fever, myalgia, arthralgia, urticaria, lymphadenopathy and gastrointestinal disorders that become evident from 7 to 15 days after antivenom administration. [15, 29] In fact immune complexes have been detected in the urine of patients administered antivenom for up to 36 days, [29] and urticarial or vasculitic rashes, arthralgias, fever, and renal dysfunction have been found to occur from these depositions. [30] How the complement system and neutrophils become activated by immune complexes is not completely understood. Some cellular receptors of complement and immunoglobulins, such as C3bR, C5aR and FcγIII, have been implicated as important participants in this activation mechanism. [10] In general, during serum sickness, laboratory analyses show elevated erythrocyte sedimentation rate, leukocytosis occasionally accompanied by eosinophilia, haematuria, proteinuria and decreased complement components in serum (e.g. C3, C4 and CH50 activity). In a recent study, it was found that after

antivenom administration, the concentration of antibodies in serum towards heterologous immunoglobulins increases from 2 times to more than 100 times, as compared to the basal values. [31]

Lo Vecchio et al. [15] report that the incidence of serum sickness following administration of Antivenin (Crotalidae) Polyvalent can be expected to exceed 50% in the 30 to 39 vial dose range, with the incidence increasing to 100% at doses of 40 or more vials. The LoVecchio study had a large number of cases (n=181) reviewed albeit in a retrospective manner while two much smaller and earlier prospective studies found that serum sickness developed in 50% (n=20) and 75% (n=8) of snakebite patients treated with Antivenin (Crotalidae) Polyvalent and for whom follow-up data were available. [32, 33] Unlike most countries Australia has a number of monovalent antivenoms that are different volumes and each vial contains antivenom that neutralises the amount of venom from the average milking of that specific snake. All Australian snake antivenoms are equine-derived polyclonal $F(ab')_2$ antivenoms that are also used in Papua New Guinea. The recommended standard dose of antivenom is one vial, although larger doses are sometimes given as dictated by the treating doctor. In this study we found no direct association between the development of serum sickness and the amount (units, equivalent to volume) of Australian snake antivenom administered. However, serum sickness was less likely to occur with the lower volume brown snake antivenom. Unfortunately the study was not large enough to show a statistically significant difference, therefore

subsequent larger studies are recommended and may find that larger volume is associated with serum sickness.

Recommendations on the treatment of serum sickness also vary. Dart and McNally mention that serum sickness may temporarily disrupt patients' activities such as the ability to work and often requires symptomatic therapy with antihistamines and systemic administration of steroids. [7] A Cochrane review (2000) concluded that based on the available evidence at the time corticosteroid treatment alone was likely to be of benefit for the treatment of delayed antivenom reactions, such as serum sickness. [34] In Australia, many guidelines recommend that serum sickness should be treated with a one-week course of corticosteroids and in severe cases an oral prednisone starting dose of 60 mg/day with tapering down over two or more weeks [35] is thought to be appropriate, although a randomised controlled trial would be necessary to confirm this.

Limitations

The main limitation of this study was our inability, given the large geographical area and often remote locations of patients, to physically assess each patient and arrange confirmatory laboratory tests at the time of the illness (presumed serum sickness). However, patient data for the Australian Snakebite Project is collected prospectively on clinical research forms by the treating health care workers and every patient who received antivenom was then followed-up by telephone at two pre-defined time points (7 to 10 days and 6 weeks after administration of the antivenom) by a single

research assistant, the data recorded onto a preformatted datasheet and then transferred to the Australian snakebite project database. This procedure captured patients with and without symptoms therefore reducing any bias associated with only unwell patients seeking treatment follow up. The definition of serum sickness had also been defined prior to the patients being prospectively followed up. The incorporation of photographic documentation of rash, swollen joints and any other specific symptom, and correlation with immunological investigations may have improved the study, and should be considered in future investigations.

Although a pre-formatted symptom collection sheet was used, this has not been validated and subsequent symptom collection sheets would benefit by incorporating outcomes such as time lost from work/school or normal activities, and hospitalisation. Some patients were difficult or unable to be contacted which may have had a small impact on final numbers, but this rarely occurred and as there was a large number of cases followed up it is believed that the data is representative of the general population. A sensitivity analysis that assumed that all patients lost to follow up did not have serum sickness, found that this only reduced the incidence to 25%.

Conclusion

Serum sickness after the administration of Australian snake antivenom is common. Just over one-quarter of envenomed patients had symptoms consistent with serum sickness. Serum sickness is most common for tiger snake and polyvalent

antivenoms, and least likely for brown snake antivenom but there was no statistical association between the volume of antivenom administered and the incidence of serum sickness. The results of this study will inform health care workers on the relative risk of serum sickness associated with Australian snake antivenom and therefore inform treatment decisions and discharge advice for patients given antivenom.

Declaration of Interest

The authors report no declarations of interest.

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