Original article

Adverse drug reaction profile of anti-snake venom in a rural tertiary care teaching hospital


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Abstract

Snake bite is a major occupational hazard to farmers, laborers especially in rural areas. Majority of the antivenom reactions are wrongly attributed to envenomation. The study was carried out with the aim of evaluation of the adverse drug reaction profile of anti-snake venom serum (ASV) in a rural tertiary care hospital.

An observational study was conducted in SRTR Medical College, Ambajogai, Maharashtra, India. A total number of 296 indoor case papers of snake bite from February to September 2011 and June to August 2012 were retrieved from the record section and the antivenom reactions were assessed. In addition, basic epidemiological data and prescribing practices of ASV were also analyzed.

Vasculotoxic snake bites were more common (50.61%) than neuroparalytic ones (22.56%). Mild envenomation was the commonest presentation. A total of 92 (56.10%) patients who received ASV suffered from antivenom reactions. The most common nature of reaction was chills, rigors (69.56%) followed by nausea and vomiting (34.8%). 10–15% patients suffered from moderate to severe reactions like hypotension and sudden respiratory arrest. We did not find any dose response relationship of ASV to risk of reactions (odds ratio 0.37). Intradermal sensitivity test was performed in about 72% cases. Our study showed a higher incidence of reactions to ASV at our institute.

The poison of snake and newt; Is sweat of “Envy’s foot”

—William Blake (Auguries of Innocence).

1. Introduction

Snake bite is a common, neglected and frequently devastating environmental and occupational disease, especially in rural areas of tropical developing countries. It is a major public health problem in India with estimated annual snake bite incidence of about 250,000 out of which approximately 20% bites result in significant envenoming which require anti-snake venom administration.

The snake bite associated morbidity is estimated to be about 1.4–68/1 lakh population, mortality about 1.1–2.4/1 lakh and case fatality rate of 1.7–20%. It is estimated that between 35,000–50,000 people die of snake bite in India each year. Early in 2009, snake bite was included in the WHO’s list of neglected tropical diseases.

Antivenom (ASV) and its rational use is the only definitive treatment to neutralize venom in circulation and in tissue fluid to save life in snake bite cases. Antivenom is an immunoglobulin usually pepsin refined F(ab)₂ fragments of IgG purified from the serum or the plasma of a horse or sheep that has been immunized with the venom of one or more species of snakes. In India only polyvalent ASV is available. The antivenins are produced against 4 most important venomous snakes of India — Naja naja (Indian cobra); Bungarus caeruleus (Indian common krait); Daboii russelli (Russell’s viper) and Echis carinatus (Saw-scaled viper). Each ml of polyvalent ASV produced in India neutralizes 0.6 mg dried Indian cobra venom, 0.45 mg dried common krait venom, 0.6 mg of dried Russell’s viper venom and 0.45 mg of dried Saw-scaled viper venom.

Usually more than 20% cases develop either early (within few hours) or late (5 days or more) allergic reactions following ASV administration. The deaths due to ASV reactions are wrongly attributed to envenomation. In addition, the significant problem of acute adverse reactions to ASV is compounded by a lack of appropriate recommendations regarding prevention, diagnosis and management of such reactions.
Considering the prevalence of snake bites and severity of the problem at rural setup the present study was planned to evaluate the adverse drug reaction profile of ASV in a rural tertiary care teaching hospital.

2. Subjects and methods

2.1. Ethics

An observational study was conducted in Pharmacovigilance Centre at Swami Ramanand Teerth Rural Govt. Medical College, Ambajogai, Maharashtra, India. The ethical approval was obtained from Institutional Ethics Committee prior to initiation of the study (SRTRMC/PHARMAC/IEC/408/2011).

2.2. Patients

Records of total number of 296 indoor cases admitted from February to September 2011 and June to August 2012 were retrieved from the medical record section of the institute and data was collected on a prevalidated case record proforma. Out of which, 164 cases in whom ASV was administered due to systemic envenomation were included in the study results. The first section of the data included demographic data like initials of patient, age, gender, weight, occupation and address. The second section was regarding the documentation of snake bite like type of snake bite, initial clinical presentation of the patient, intradermal sensitivity test done or not, 20 min whole blood clotting test (WBCT), dose, route and frequency of administration of ASV.

2.3. Signs of adverse reactions

The antivenom reactions were documented and classified as early anaphylactic, endotox (pyrogenic) and late (serum sickness type) reactions. The management of antivenom reactions was also recorded. The data was filled on suspected adverse drug reaction reporting form by Central Drug Standard Control Organization. The reactions were assessed by seriousness (death, life threatening, hospitalization-initial or prolonged, disability and required intervention to prevent permanent damage/impairment) and outcome (fatal, continuing, recovered and recovering). The outcome of the cases was analyzed under headings of recovery, referral and mortality.

3. Results

3.1. Patient demographics

Out of the 164 patients who received antivenom, 91 (55.49%) were male and 73 (44.51%) female. This can be attributed to the out-dwelling lifestyle and occupational outdoor stay of males. Incidence of snake bite was most common in the age group of 21–30 years (27.36%), followed by 31–40 years and 11–20 years (20.27%). The majority of patients were farmers, plantation workers and laborers (Table 1). The incidence of antivenom reactions was highest in the age group of 21–40 years (Table 2). We found the incidence of vasculotoxic snake bites was more common (50.61%) than neuroparalytic snake bites (22.56%).

3.2. Antivenoms used, dosage forms and routes of administration

The anti-snake venom used at our setup during the study duration was manufactured by, Haffkine Biopharmaceutical Company Ltd. Mumbai, VINS Bioproduct Ltd. Hyderabad and Bharat Serum and Vaccines Ltd. Mumbai. The lyophilized antivenom was reconstituted with 10 ml water to 10 ml of ASV. The dose of ASV largely depends upon the signs of systemic envenomation and severity of bite. In our setup the dose of ASV used ranges from 50 cc to 200 cc depending upon signs and symptoms of the patient. The most commonly used loading dose of antivenom was 100 ml. The ASV was diluted and infused intravenously at a constant rate over a period of about one hour (Fig. 1).

3.3. Intradermal skin testing to predict antivenom reaction prior to administration of ASV

Skin/conjunctival hypersensitivity testing does not reliably predict early or late antivenom reactions as they are mediated by direct activation of complement system and not mediated by IgE and is not recommended. However in our study, we found that in about 72% of cases the skin hypersensitivity test was performed prior to initiation of ASV therapy. Skin testing only delays the administration of ASV and can themselves be sensitizing.

3.4. Adverse antivenom reaction rates

A total of 92 patients (56.10%) who received ASV suffered from antivenom reactions. The most common presentation of reaction were chills, rigors (69.3%) followed by nausea and vomiting (41.3%). 10–15% patients suffered from moderate to severe reactions like hypotension and sudden respiratory arrest (Fig. 1). The literature by WHO states that the antivenom reactions are dose related, however in our study we did not find any statistically significant dose response relationship of ASV to risk of reactions (odds ratio 0.37) (Fig. 2). Some investigators believe that ASV reactions are seen more in hemotoxic bites than neurotoxic ones. In our study, there was a higher incidence of antivenom reactions in cases of vasculotoxic snake bites (52.17%) as compared to neuroparalytic snake bites (21.74%) (Table 3).

### Table 1

Demographic details of patients admitted with snake bite.

<table>
<thead>
<tr>
<th>Age (in years)</th>
<th>No. of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–10</td>
<td>6</td>
</tr>
<tr>
<td>11–20</td>
<td>60</td>
</tr>
<tr>
<td>21–30</td>
<td>81</td>
</tr>
<tr>
<td>31–40</td>
<td>60</td>
</tr>
<tr>
<td>41–50</td>
<td>42</td>
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<tr>
<td>51–60</td>
<td>24</td>
</tr>
<tr>
<td>&gt;60</td>
<td>23</td>
</tr>
</tbody>
</table>

### Table 2

Age and gender wise distribution of antivenom reactions.

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Gender</th>
<th>Reaction present</th>
<th>Reaction absent</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number</td>
<td>%</td>
<td>Number</td>
<td>%</td>
</tr>
<tr>
<td>≤20</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>14</td>
<td>15.22</td>
<td>12</td>
<td>66.67</td>
</tr>
<tr>
<td>Female</td>
<td>11</td>
<td>11.96</td>
<td>8</td>
<td>11.11</td>
</tr>
<tr>
<td>21–40</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>17</td>
<td>18.48</td>
<td>18</td>
<td>25.00</td>
</tr>
<tr>
<td>Female</td>
<td>23</td>
<td>25.00</td>
<td>12</td>
<td>16.67</td>
</tr>
<tr>
<td>41–60</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>6</td>
<td>6.52</td>
<td>14</td>
<td>19.44</td>
</tr>
<tr>
<td>Female</td>
<td>13</td>
<td>14.13</td>
<td>3</td>
<td>4.17</td>
</tr>
<tr>
<td>&gt;60</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>5</td>
<td>5.43</td>
<td>5</td>
<td>6.94</td>
</tr>
<tr>
<td>Female</td>
<td>3</td>
<td>3.26</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>92</td>
<td>72</td>
<td>296</td>
<td></td>
</tr>
</tbody>
</table>
3.5. Characteristic features of snake bites

Mild envenomation was the commonest presentation. The commonest symptoms of presentation was swelling at site of bite in case of vasculotoxic bite and drooping of eyelid in case of neuroparalytic snake bite. The commonest site of bite was found to upper limb in case of female and lower limb in case of male. The average journey time to hospital (AJTH) was 3 h. The mean duration of hospitalization was 3 days; with outcome of more than 89% patients was recovered.

4. Discussion

Snake bite is a common occupational hazard of farmers, plantation workers who are generally from low socio-economic status, resulting in tens of thousands of deaths each year and many cases of chronic physical handicap.

4.1. Role of antivenom

The only specific antidote to the toxins in snake venom is hyperimmune globulin from an animal that has been immunised with the appropriate venom.\textsuperscript{11} The introduction of serum antivenom by Albert Calmette in 1895 for the treatment of envenoming was quickly accepted without formal clinical trials.\textsuperscript{12} More than a century later, antivenoms are considered as essential drugs.

ASV is prepared from horse serum and is associated with allergic reactions which may result in anaphylaxis and even death. It is costly and there is a constant shortage of ASV, particularly in rural and underdeveloped parts of India. Thus ASV should be used only when there is possibility of circulating venom in the body and not to all snake bite cases. However, early administration of ASV is essential to neutralize the maximum circulating venom before it is fixed in the tissue. Therefore, it should be given to cases with evidence of systemic envenomation as early as possible. Development of enlarged tender lymph node draining the bitten limb is an early manifestation of poisonous snake bite needing ASV therapy.

4.2. Adverse reactions to antivenom and its prevention and treatment

4.2.1. Early anaphylactic reactions

It usually occurs in 10—180 min of starting antivenom. It includes urticaria, itching (often over the scalp), cough, nausea, vomiting, abdominal colic, diarrhea and tachycardia. Minority of cases present with fatal anaphylaxis-hypotension, bronchospasm and angioneuritic edema. They occur due to direct activation of complement by IgG and residual FC fragment or direct stimulation of mast cells and basophils by antivenin proteins. They are not IgE mediated, type I reactions.

4.2.2. Pyrogenic reactions

It usually develops 1—2 h after starting ASV therapy. Fever, rigors, chills, hypotension are the presenting features. They are due to pyrogenic contamination of ASV and diluting fluid.

4.2.3. Late serum sickness type reactions

It develops in 1—12 days after antivenin therapy (mean 7 days). Clinical features include fever, nausea, arthralgia, myalgia, arthritis, mononeuritic multiplex, recurrent urticaria, lymphadenopathy.

<table>
<thead>
<tr>
<th>Type of snake bite</th>
<th>Reaction to anti-snake venom</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Present</td>
</tr>
<tr>
<td>Vasculotoxic</td>
<td>48</td>
</tr>
<tr>
<td>Neuroparalytic</td>
<td>20</td>
</tr>
<tr>
<td>Not specified</td>
<td>24</td>
</tr>
<tr>
<td>Total</td>
<td>92</td>
</tr>
</tbody>
</table>

Table 3

Reaction profile according to types of snake bite.

Fig. 1. Frequency of antivenom reactions.

Fig. 2. Dose response to ASV in terms of ADR.

Fig. 3. Ptosis in neuroparalytic snake bite.
neuritis and even encephalopathy. They usually respond to oral antihistamine.

Our study showed a higher incidence of reaction to ASV as compared to WHO literature, most of which were of early anaphylactic type or pyrogenic (endotoxin) in nature. Majority of the reactions were classified as “not preventable” by Schumock Thornton criteria. They were “expected”, “hypersensitivity reactions” as per Karch and Lasanga classification of adverse drug reactions. With the use of modified Hartwig Siegel scale, majority of the antivenom reactions were mild and moderate in nature. The antivenom reactions were treated with adrenaline, anti-histaminics and steroids. There was a trend of using prophylactic anti-histaminics and corticosteroids in anticipation of reactions. Attempts to prevent early reactions which include pretreatment with epinephrine, anti-histaminics, corticosteroids and reduction in speed and concentration of intravenous antivenom administration have not been effective in adequately designed clinical trials.13, 14, 15 However the studies by Premawardhena et al16 Gawarammana et al17 and de Silve et al18 have shown the efficacy of low dose adrenaline and combination of chlorphenamine and hydrocortisone in reduction of antivenom reactions. A recent systematic review and meta-analysis19 has shown the beneficial role of premedication with adrenaline in reduction of early antivenom reactions. Epinephrine is the most promising treatment for anaphylactic reactions, acts by reducing the capillary permeability and bronchospasm. However, the risks of epinephrine make it less attractive as a prophylactic treatment.20, 21 In presence of such controversial data, the WHO has not recommended routine use of prophylactic drugs to prevent ASV induced reactions. In the absence of any proven effective method of prevention of antivenom reactions, patients should be observed carefully for at least 2 h after they are given antivenom, and epinephrine should be given at the first sign of anaphylaxis. Also, there was a poor documentation of adverse drug reactions to ASV in terms of onset, duration, outcome and seriousness.

4.2.4. 20 min whole blood clotting test (20 WBCT)

This very useful and informative bedside test requires very little skill and one apparatus-clean, dry glass vessel. If the blood is still liquid (un-clotted) after 20 min and runs out, the patient has hypofibrinogenaemia as a result of venom induced consumption coagulopathy. This test is important parameter for initiation and repetition of ASV in snake bite cases. In India whole blood clotting time of more than 20 min is virtually diagnostic of viper bite and coagulopathy. This test is important parameter for initiation and seriousness.

In conclusion, the management practices of snake bite cases and adverse drug reactions following ASV administration are far from satisfactory in our institute. There is a need of adequate documentation of adverse reactions in terms of onset, duration, severity and outcome. Also, there is underreporting of antivenom reactions of ASV to the Pharmacovigilance Centre at our institute. It is partly due to absence of efficient ADR monitoring system and partly because of lack of reporting culture among the treating physicians. It is a need of hour for Pharmacovigilance training in the form of CMEs or Workshops to the treating physicians for better diagnosis and reporting of adverse drug reactions.

This study provides insight into current clinical management of snake bite in rural health centers and provides incidence and severity of antivenom reactions. We plan to use the results of this study to conduct a prospective trial for antivenom premedication strategies in India.

Conflicts of interest

All authors have none to declare.

References


