Use of antivenom for snakebites reported to United States poison centers

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Abstract In 2001, a new antivenin was introduced to the United States and became widely available in the snakebite season of 2002. We investigated what impact this may have had on snakebite treatment and medical outcome.

Method: The study used a retrospective review of all snakebites to humans reported to the National Poison Center Database System from 2000 to 2007.

Results: During the 8 years, there were 37,760 snakebites, with a mean of 4720 bites per year. There was a 27% increase in bites reported to a Poison center for the 8-year period and an overall 13.5% increase in the use of antivenin. The 2 categories primarily responsible for the increased use of antivenin were copperhead and crotaline-unknown. Rattlesnake bites remained the category most frequently treated with antivenin with a mean 52.5% treatment rate and only moderate increase for the 8 years. There was no change in the percentage or number of patients with a major outcome (mean, 3.8%) or death (mean, 0.5%). There was a decrease in patients with a minor outcome and an increase in patients with a moderate outcome.

Discussion: The new antivenin is reported to have a reduced potential for adverse reactions. This may have had a role in the decision of which snakebite victims received antivenin.

Conclusion: With the introduction of a new antivenin, there has been a dramatic increase in the number of snakebite patients treated with antivenin. This has been most noticeable in snake bite categories that were less frequently treated with antivenin in the past.

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1. Introduction

Venomous snake bite remains a common event in the United States [1]. Historically, treatment has varied in different regions of the United States, particularly with respect to the use of antivenom. Important factors involved in the decision to use antivenom have included the clinical effects present in the patient, the suspected snake species involved and the specific antivenom available for use.

Before the year 2000, the primary antivenom available in the United States for pitviper bites was the Wyeth (Madison, NJ, USA) (Crotalidae) polyvalent antivenin, a whole IgG antivenom (equine), obtained from fractionating blood from horses that had been injected with extracted venom of 4 snake species [2]. This product was successful in treating snakebites but was often reserved for more severe bites, such as rattlesnake bites, due to a reported high rate of adverse effects, particularly anaphylactoid reactions and serum
sickness [3]. In 2000, the Food and Drug Administration approved a new antivenom that was expected to reduce the incidence of severe adverse reactions. Crotalidae polyvalent immune Fab (ovine) (CroFab) (Melville, NY, USA) is a mixture of 4 monospecific antivenoms that use only the Fab fragment of the IgG antibody [4]. The new antivenom does not contain the antigenic Fc antibody fragment, which is felt to play a significant role in the development of immunologic reactions [5,6]. One difference of the new antivenom is that it uses venom from the Agkistrodon group, which are the predominant genera in the eastern United States. CroFab includes venom from the 4 snakes Crotalus atrox (Western diamondback rattlesnake), Crotalus adamanteus (Eastern diamondback rattlesnake), Crotalus scutulatus (Mojave rattlesnake), and Agkistrodon piscivorus (cottonmouth).

We decided to investigate whether the introduction of a new antivenom had an impact on the treatment and medical outcome of snakebites in the United States. Because snake species and snakebites have specific geographic ranges, we also investigated whether there have been any significant regional shifts in how these cases are managed.

### 2. Methods

This was a retrospective review of all venomous snakebites reported to the National Poison Center Database System (NPDS) of the American Association of Poison Control Centers from 2000 to 2007. CroFab was not available in 2000 allowing a view of management of snakebites before its release. In addition, due to production problems, there was very limited distribution of CroFab in 2001. The production of Wyeth (Crotalidae) polyvalent antivenom ceased in 2000, and with a shelf life of 3 years, the data from 2004 and later reflect primarily use patterns with the newer antivenom.

Inclusion criteria included human patients, with a route of exposure of bite/sting and substance categories of rattlesnake envenomation, copperhead envenomation, coral snake envenomation, unknown crotalid envenomation, southern copperhead envenomation, unknown type of snake envenomation (unknown if poisonous), exotic snake (not indigenous to the United States)—poisonous, and exotic snake (not indigenous to the United States)—unknown if poisonous. Exclusion criteria were animal victims and snakebites identified as nonpoisonous.

The definitions for medical outcome were the standard definitions used by NPDS as follows: no effect (no signs or symptoms as a result of the exposure), minor effect (signs or symptoms were minimally bothersome and resolved rapidly), moderate effect (signs or symptoms were more pronounced, more prolonged, or more systemic in nature, usually requiring treatment but not life-threatening), major effect (signs or symptoms were life-threatening or resulted in significant residual disability), or death (death resulted from the exposure or direct complication of the exposure).

### Table 1

<table>
<thead>
<tr>
<th>Snake type</th>
<th>2000</th>
<th>2001</th>
<th>2002</th>
<th>2003</th>
<th>2004</th>
<th>2005</th>
<th>2006</th>
<th>2007</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of bites (% of total bites)</td>
<td>No. of bites (% of total bites)</td>
<td>No. of bites (% of total bites)</td>
<td>No. of bites (% of total bites)</td>
<td>No. of bites (% of total bites)</td>
<td>No. of bites (% of total bites)</td>
<td>No. of bites (% of total bites)</td>
<td>No. of bites (% of total bites)</td>
<td>No. of bites (% of total bites)</td>
</tr>
<tr>
<td>Rattlesnake</td>
<td>1008 (25.8)</td>
<td>1133 (27.4)</td>
<td>1158 (25.2)</td>
<td>1110 (20.9)</td>
<td>1048 (20.9)</td>
<td>1413 (28.1)</td>
<td>193 (3.8)</td>
<td>141 (2.9)</td>
<td>7810</td>
</tr>
<tr>
<td>Copperhead</td>
<td>707 (18.1)</td>
<td>763 (18.4)</td>
<td>794 (18.4)</td>
<td>354 (7.7)</td>
<td>291 (7)</td>
<td>396 (8)</td>
<td>428 (8.5)</td>
<td>404 (8.2)</td>
<td>3997</td>
</tr>
<tr>
<td>Unknown crotalid</td>
<td>100 (2.6)</td>
<td>134 (3.2)</td>
<td>171 (3.5)</td>
<td>172 (3.5)</td>
<td>192 (3.8)</td>
<td>193 (3.8)</td>
<td>199 (4)</td>
<td>1161 (23.8)</td>
<td>247</td>
</tr>
<tr>
<td>Cottonmouth</td>
<td>1675 (42.4)</td>
<td>1630 (39.9)</td>
<td>1620 (35.4)</td>
<td>1610 (34.9)</td>
<td>1904 (38.5)</td>
<td>1910 (39.3)</td>
<td>1708 (35.2)</td>
<td>1708 (35.2)</td>
<td>13766</td>
</tr>
<tr>
<td>Unknown</td>
<td>67 (1.7)</td>
<td>66 (1.6)</td>
<td>84 (1.8)</td>
<td>59 (1.2)</td>
<td>66 (1.3)</td>
<td>58 (1.2)</td>
<td>96 (1.9)</td>
<td>96 (1.9)</td>
<td>963</td>
</tr>
<tr>
<td>Coral snake</td>
<td>70 (1.8)</td>
<td>64 (1.6)</td>
<td>123 (2.7)</td>
<td>123 (2.7)</td>
<td>98 (1.9)</td>
<td>98 (1.9)</td>
<td>98 (1.9)</td>
<td>98 (1.9)</td>
<td>704</td>
</tr>
<tr>
<td>Nonindigenous snake</td>
<td>98 (2.5)</td>
<td>98 (2.5)</td>
<td>98 (2.5)</td>
<td>98 (2.5)</td>
<td>98 (2.5)</td>
<td>98 (2.5)</td>
<td>98 (2.5)</td>
<td>98 (2.5)</td>
<td>98</td>
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<tr>
<td>Total</td>
<td>3911</td>
<td>4136</td>
<td>4602</td>
<td>4974</td>
<td>4974</td>
<td>4974</td>
<td>4974</td>
<td>4974</td>
<td>37760</td>
</tr>
</tbody>
</table>
Data provided to NPDS on cases include the following: demographics (age, sex) of patient, date and state of occurrence, substance involved in the poisoning, clinical effects, therapies provided, site of patient management, and medical outcome. Statistics used were primarily descriptive. \( \chi^2 \) 2-Tailed test was used to evaluate change of antivenom use change over the study period.

3. Results

3.1. Demographics

During the 8 years, there were 37,760 snakebites reported to NPDS, of which 27,328 (72.4%) were male. There was a mean of 4,720 bites per year, with an overall 27% increase in reported snakebites between 2000 and 2007. During this same 8-year period, there was a 14.5% increase in total human poison exposure case reported to NPDS, so the increase in snakebite cases in NPDS may partially reflect increased use of US poison centers. The most commonly identified snake group was the rattlesnakes, followed by the copperheads. A substantial minority of bites occurred from snakes that were not identified (Table 1). Snakebites in the United States occurred most frequently in the southern states with the warmer climates, and 15 states (30%) were responsible for 78% of the snakebites reported (Table 2).

3.2. Antivenom use

For the 8-year period, there was an overall increase in the use of antivenin of 13.5%—from 743 patients (19%) in 2000 to 1,617 patients (32.5%) in 2007 (\( P < .001 \); see Table 3). The 2 categories primarily responsible for the increased use of antivenin were copperhead and crotaline-unknown. \( (R^2 \text{ value, linear regression}, 0.964 \) and 0.931, respectively) (Table 3, Fig. 1). Rattlesnake bites remained the category most frequently treated with antivenin with a mean 52.5% treatment rate and a more moderate increase for the 8 years. Adverse reaction to antivenin therapy decreased steadily during the first 4 years of the study period from 5.8% in 2000 and plateaued at approximately 3%, after the Wyeth (Crotalidae) polyvalent antivenin was no longer available (Fig. 2).

3.3. Medical outcome

For this 8-year period, there was no change in the annual number or percentage of patients with a major outcome (mean, 180 patients and 3.8%, respectively) or death (mean, 2 patients and 0.5%, respectively). There was a decrease in patients with a minor outcome from 36.4% to 31.7% and an increase in patients with a moderate outcome from 29.2% to 37.7% (Fig. 3). Because of the significant increase in number and percentage of copperhead bite patients treated with antivenin, we evaluated the medical outcome of copperhead bite patients separately (Fig. 4). Despite a greater than 3-fold increase in use of antivenin, medical outcome as measured by NPDS remained unchanged. Evaluation of other specific snakebite groups (cottonmouth, crotaline-unknown, and rattlesnake) showed similar findings.

4. Discussion

Introduction of a new Fab-fragment antivenin coincided with a consistent increase in the number of patients treated...
annually with antivenom (19% of patients to 33% of patients).
The most significant increase in use has occurred in snakebites that were previously less commonly treated with antivenom, including copperheads (10%-36%), unknown crotaline (19%-41%), and cottonmouth (18% to 29%). One possible reason for the increased use in these groups is the reported reduced potential for adverse reactions with the new Crotalidae polyvalent immune Fab. The *Agkistrodon* group produces less risk of coagulopathy than the rattlesnake group, with predominantly local tissue injury, edema, and pain [7,8]. In the past, the risk of anaphylaxis from the use of Wyeth (Crotalidae) polyvalent antivenom was weighed against the potential benefit of reduced local tissue damage in the *Agkistrodon* group, and it was infrequently used. It appears that with the introduction of the new antivenom, this risk/benefit decision may have shifted more in favor of use of antivenom in these snakebite groups.

The new antivenom is reported to have a reduced potential for adverse reactions [5,6,9]. The introduction of the new antivenom coincided with a reduction of adverse reactions reported to NPDS from 5.8% to 3%. After the exhaustion of the remaining stores of the Wyeth antivenom in 2004, the rate of adverse reaction to therapy remained at 3%. An important note of caution should be made when evaluating this reported rate of adverse reactions. The rate of adverse reactions to antivenom therapy reported to NPDS is significantly lower than those previously reported in the published literature [1,3]. One study of 42 patients receiving the CroFab reported 14% of patients (6/42) experienced an adverse reaction to therapy [10]. Of these 6 patients, 4 were mild reactions with 2 requiring no pharmacologic or medical intervention and 2 (4.8%) were moderate reactions. This rate of moderate reaction is closer to the rate reported in NPDS. It should be noted that 5 of the 6 patients with adverse reaction in this study received an improperly purified batch of antivenom that contained excessive amounts of the Fe fragment, which may have contributed to the increased adverse reaction rate [9]. It seems reasonable to suggest that those adverse reactions to

<table>
<thead>
<tr>
<th>Year</th>
<th>Copperhead (%)</th>
<th>Crotaline Unknown (%)</th>
<th>Cottonmouth (%)</th>
<th>Rattlesnake (%)</th>
<th>Coral Snake (%)</th>
<th>Total Snakebites (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2000</td>
<td>26%</td>
<td>25%</td>
<td>28%</td>
<td>30%</td>
<td>25%</td>
<td>28%</td>
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<tr>
<td>2001</td>
<td>22%</td>
<td>24%</td>
<td>26%</td>
<td>28%</td>
<td>24%</td>
<td>26%</td>
</tr>
<tr>
<td>2002</td>
<td>20%</td>
<td>22%</td>
<td>24%</td>
<td>26%</td>
<td>22%</td>
<td>24%</td>
</tr>
<tr>
<td>2003</td>
<td>18%</td>
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<td>22%</td>
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<td>20%</td>
<td>22%</td>
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<td>2004</td>
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<td>2005</td>
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<td>2006</td>
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<td>18%</td>
<td>14%</td>
<td>16%</td>
</tr>
<tr>
<td>2007</td>
<td>10%</td>
<td>12%</td>
<td>14%</td>
<td>16%</td>
<td>12%</td>
<td>14%</td>
</tr>
</tbody>
</table>

OR indicates odds ratio; CI, confidence interval.

Fig. 1 Percentage of patients treated with antivenom by snake type.
antivenom therapy reported to NPDS may reflect the more remarkable cases that might require intervention or initiate a consult with a poison center on possible changes in therapy.

The geographic changes in the decision to use antivenom therapy after a snakebite are likely related to the snake species native to those states. The greatest changes tended to occur in states east of the Mississippi River, where the copperhead snake is responsible for most venomous snakebites, whereas the lowest rate of change tended to occur in western states where the rattlesnake group tends to be the predominant venomous snakebite.

In the 8 years of study, reported fatalities and life-threatening effects remained rare from snakebite in the United States. In contrast to mortality, morbidity from snakebite remains common with more than 40% of patients experiencing a serious medical outcome (moderate or major effect). This persistent level of severity occurred despite a significant increase in the use of antivenom. There was a consistent trend in increased number and percentage of cases with a moderate outcome, despite a doubling in the use of antivenom. There may have been an increased use of antivenom because of increased recommendation of the toxicologists at the poison centers or an increase in the severity of bite reported for the 8-year period. Medical outcome in NPDS is recorded as the highest level of morbidity reported. However, it does not record duration of morbidity. This is important because morbidity from snakebite tends to persist for weeks to months [8]. Increased antivenom use may have reduced the duration of morbidity in patients who received antivenom therapy, and NPDS data would not reflect that change. Studies on the impact of antivenom on the reduction of duration of morbidity from snakebite may be warranted.

It is unclear why there was an increase in moderate outcomes with a subsequent decrease in minor outcomes, despite the increase in the use of antivenom. There are several potential factors that may have had a role in this change. The first possible factor is that there may have been a change over the years of the study period in coding habits of the specialists that document these cases at poison centers. Our data showed a relative 29% increase (29.2% in 2000 to 37.7% in 2007) in outcomes coded as moderate, whereas the total NPDS data for all poisoning categories showed a 13% increase (4.6% in 2000 to 5.2% in 2007). A similar change was noted in those cases coded as a minor outcome. In our data set of snakebites, we saw a relative decrease of 13% in minor outcomes (36.4% in 2000 to 31.3% in 2007), and in the total NPDS data for all poisoning categories, the decrease was 9% (15.6% in 2000 to 14.2% in 2007). A second possible factor might be that there was a decrease in the percentage (4%) of cases with a snakebite that were reported as having no follow-up to a known outcome. However, it seems unlikely that the entire number of patients with increased follow-up would all shift to the moderate outcome category. In addition, this number of cases is insufficient to explain the larger number of cases with a moderate outcome. A third possible factor is that the increase in moderate outcomes is due to the increase in the total number of bites that were reported to poison centers over the period of study. This would suggest that most of the increase in number of bites reported were all shifted to the moderate outcome category. Finally, there is the potential that the specialist recording the case data may have been more likely to code...
the case as a moderate outcome if antivenom had been used as opposed to if antivenom had not been used.

There are a number of limitations to this study. This was a retrospective study and necessarily reflects the limitations associated with retrospective data collection. There was no outcome data on approximately 20% of the reported snakebites. Most of these cases without a known outcome were for a group of snakes recorded as “unknown snake,” and it is unclear how many of these patients went on to be treated at a health care facility and specifically to receive antivenom therapy. However, we believe it is unlikely that a significant number of these patients received antivenom. In the 9767 patients in the “unknown snake” group with a known medical outcome (67%), 968 received antivenom therapy (9.9%). This group of snakes was the least likely snakebite group to receive antivenom in this study. National Poison Center Database System is a passive data collection system and requires the caller to seek the advice of a poison center to be recorded. It is unknown how many snakebites occurred where the consultation of a poison center was not sought and therefore was not recorded in NPDS. Finally, the data provided to NPDS do not include the case notes from the patient record, which might have clarified timing or progression of clinical effects or discussions about the clinical decision to administer the antivenom. The data do not allow determination of whether the antivenom was needed by the patient, only whether it had been administered. Despite these limitations, this study reports on the largest group of snakebites available.

5. Conclusion

With the introduction of a new antivenin, there has been a dramatic and consistent increase in the number of snakebite patients treated with antivenom. This has been most noticeable in snakebite categories that were less frequently treated with antivenom in the past. There was no change in the rate of death or serious outcomes. The ability of this retrospective study to make conclusions about subtle changes in outcome is limited.

References