Management of Viper bites in Europe.

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Introduction:

Several species of vipers of the genus *Vipera*, *Macrovipera* or *Montivipera* live in Europe.

*Vipera berus*, *V. ammodytes* and *V. aspis* are the 3 species which cause the highest number of human envenomations in this continent.
From Chippaux, Toxicon 2011
EPIDEMIOLOGY

Recent epidemiological data: every year in the whole of Europe (including European Turkey and Russia up to the Urals and the Caucasus, representing 750 million people) around 7500 viper bites occur including approximately 1000 severe envenomations and less than 5 deaths (Chippaux, Toxicon 2011).
Situation in Europe

Z = zero, R = rare event, NE = not exceptional
Seasonal prevalence of snakebites in Europe (Chippaux, Toxicon 2011)
Clinical feature of viper bite in Europe:

- immediate and intense pain
- swelling in few minutes

- 10 to 15% of the patients will present an increase of the symptoms due to the venom diffusion: Extensive swelling, systemic symptoms, biological troubles.

Spontaneous evolution of such a case: life-threatening situation.
As the clinical features of viper envenomation are relatively homogenous through Europe, the gradation table published in 1992 by the Pasteur Institute of Paris is considered as pertinent for evaluating the viper bite severity at the continental level.

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
<th>Symptoms</th>
<th>Venom Concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>G0</td>
<td>Dry bite</td>
<td>Fang marks</td>
<td>$1 \pm 0.3 \text{ ng/ml}$</td>
</tr>
<tr>
<td>G1</td>
<td>Mild envenomation</td>
<td>Local swelling</td>
<td>$5 \pm 1.8 \text{ ng/ml}$</td>
</tr>
<tr>
<td>G2</td>
<td>Moderate envenomation</td>
<td>Extensive swelling and/or general signs</td>
<td>$32 \pm 7 \text{ ng/ml}$</td>
</tr>
<tr>
<td>G3</td>
<td>Severe envenomation</td>
<td>Body swelling + severe general symptoms</td>
<td>$126 \pm 50\text{ ng/ml}$</td>
</tr>
</tbody>
</table>
Consensus for treatment for viper envenomations in France:

G0 and G1: symptomatic treatments only
G2 and G3: Antivenom Viperfav* IV

- Good efficacy on general and local symptoms
- Excellent tolerance
- Made with horse antibodies against *Vipera aspis*, *Vipera berus* and *Vipera ammodytes* (Eastern Europe)
Epidemiological data concerning viper bites in France:

- 2008, congress of the French Society of Clinical Toxicology: study of the number of viper bite managed by the 10 French poison centres during 2007. 979 viper bites including 95 grade 2 or 3 with antivenom treatment required.

- 2010 : 3 studies published in France, Toulouse, Angers and Marseille.

- Toulouse: 2008 and 2009, 83 viper bites including 27 grade 2 and 11 grade 3. (Cordier et al. STC congress, May 2010) That means that 38 patients needed antivenom BUT only 12 patients were really treated (30 % !!).
Epidemiological data concerning viper bites in France:

- Study in Angers Poison Centre in 2010
  (Boels et al., Toxicon 2012, EAPCCT abstract published in Clin Tox 2010).

- Between 1999 and 2008, 621 bites.
- 268 patients treated with antivenom (214 grade 2 and 54 grade 3).
  No precisions on the % of G 2 and 3 who did not receive antivenom.

Excellent tolerance:
- Zero anaphylactic reaction
- 2 mild serum sickness reaction
Conclusions of the Angers Poison Centre study:

- Delay before Viperfav infusion <10 hours
  - reduces the length of hospital stay
  - reduces persistent functional impairment
  - reduces the incidence of haematoma
- A single dose of Viperfav™ is effective whatever severity of envenomation.
- The safety of Viperfav™ is excellent.
- Heparin increases the length of hospital stay and persistence of functional impairment.
- Corticosteroids and antibiotics are not systematically indicated.
Epidemiological data in France:

- Study in Marseille Poison Centre in 2009 (de Haro et al., Toxins 2009; 1:100-12).

- 90 grade 2 and 32 grade 3.
- 106 patients treated with the Viperfav* antivenom

Excellent tolerance:
- Zero anaphylactic reaction
- Zero serum sickness reaction

*Viperfav* refers to the Vipera aspis antivenom.

Toxins 2009, 1, 100-112; doi:10.3390/toxins1020100

Asp Viper (Vipera aspis) Envenomation: Experience of the Marseille Poison Centre from 1996 to 2008

Luc de Haro *, Mathieu Glaizal, Lucia Tichadou, Ingrid Blanc-Brisset and Maryvonne Hayek-Lanthois
Annual distribution

Seasonal distribution

Grade 2+3 with or without antivenom
Description of 174 cases of viper bites managed by the Marseille Poison Centre between 1996 and 2008 inclusive.

<table>
<thead>
<tr>
<th>Grade</th>
<th>n</th>
<th>Child / adult</th>
<th>Neuro-toxic signs</th>
<th>Place of medical management</th>
<th>Anti-venom</th>
<th>Evolution</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Home</td>
<td>Emerg</td>
<td>Spe. U</td>
</tr>
<tr>
<td>1</td>
<td>52</td>
<td>12/40</td>
<td>0</td>
<td>8%</td>
<td>92%</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>90</td>
<td>28/62</td>
<td>11 (12%)</td>
<td>0</td>
<td>77%</td>
<td>13%</td>
</tr>
<tr>
<td>3</td>
<td>32</td>
<td>8/24</td>
<td>3 (9%)</td>
<td>3%</td>
<td>0</td>
<td>3%</td>
</tr>
<tr>
<td>Total</td>
<td>174</td>
<td>48/126</td>
<td>14 (8%)</td>
<td>3%</td>
<td>67%</td>
<td>6%</td>
</tr>
</tbody>
</table>

* There is no significant difference in the grade distribution between adults and child patients with a Chi2 statistical test.

** One patient died in few minutes after the bite by direct intravascular venom injection, and before any medical management.
Duration of envenomed patient hospitalization with or without antivenom treatment.

<table>
<thead>
<tr>
<th>Grade</th>
<th>Average hospitalization duration (days)</th>
<th>Total (days) Without/With antivenom</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No antivenom</td>
<td>1 infusion</td>
</tr>
<tr>
<td>1</td>
<td>0.96 ± 0.8</td>
<td>NA</td>
</tr>
<tr>
<td>2</td>
<td>6.8 ± 3.6</td>
<td>1.9 ± 0.8</td>
</tr>
<tr>
<td>3</td>
<td>10.6 ± 4</td>
<td>3 ± 0.8</td>
</tr>
<tr>
<td>2 + 3</td>
<td>8.1 ± 4</td>
<td>1.9 ± 0.9</td>
</tr>
</tbody>
</table>
Conclusions of the Marseille Poison Centre study:

- A single dose of Viperfav™ is effective whatever severity of envenomation
- The safety of Viperfav™ is excellent
- When confronted with life-threatening envenomations, there is no strong argument to justify the non-use of this antidote
- High percentage of neurotoxic envenomations in southeastern France.
The neurotoxic viper captured near the City of Nice in 1991

1 - V.a.aspis Vendée
2 - V.a.aspis Nice
3 - V.a.zinnikeri
4 - V.latastei
5 - V.ursinii
6 - V.seoanei
7 - V.am.ammodytes
8 - V.berus
For the patients management:

The antivenom Viperfav* is efficient (cross-reaction with antibodies against ammoditoxins).
The presence of neurotoxic symptoms = grade 2
More results about neurotoxicity:

- The neurotoxic population in South-Eastern France is expending as the envenomation that we observe since the beginning of the 2000s in 2 French counties are all with neurotoxic symptoms.

- 2 new populations of neurotoxic vipers of a different Sub-species (Vipera aspis zinnikeri) are now well described in 2 other French counties (south of “Lozère”, West of “Puy-de-Dôme”). Studies continue for the description of the implicated neurotoxins... A new case in summer 2010 in a new concerned county near Spain!

- The French example allowed to do the same studies in Italy were 5 neurotoxic populations of Vipera aspis francisciredi have been described.
More results about neurotoxicity:
- Recent descriptions of neurotoxic symptoms after bites of *Vipera berus* subspecies (*V.b.berus* and *V.b.bosniensis*) in Hungary (Malina 2008 and 2011), in Bulgaria (Westerström 2010) and Romania (Gafencu, EAPCCT 2012).
More results about neurotoxicity:

- A recent study (Neil et al, 2012) described a case of proved Guillaine-Barré syndrome after a *Vipera aspis aspis* bite: the asp viper came from the Southern French Alps and had no neurotoxins in its venom. The neurological clinical feature was the consequence of an autoimmune reaction (cross-reaction between GM2 ganglioside and glycosidic epitopes of the concerned asp viper venom) of the patient who was not treated with specific antivenom even though it was a grade 2 envenomation.
**MEDICAL MANAGEMENT**

First aid at the scene immediately after the bite:

- Immobilize the victim so as not to spread the venom. If the bite takes place in a remote area, the victim can be carried (children) or left at the scene (preferably in the company of another person).
- Remove tight clothing and jewelry to avoid compression due to swelling, and disinfect the wound.
- A loose fitting bandage may be applied from the root to the tip of the affected limb in order to impede spreading of the venom. There should be enough space for a finger between the skin and bandage. When in doubt about the ability to apply bandaging properly, it is better to do nothing than to risk creating an ischemic effect.
What not to do:
Do not restrict circulation by applying a tight band or tourniquet. Do not promote spread by administering drinks that increase heart rate (coffee or tea), performing mutilating acts such as wound incisions, suctioning, or cauterization. Antivenom should not be administered without medical supervision.

What is not useful:
Immediate use of heparin or its derivatives is unnecessary. Injection of low-molecular weight heparin may promote spread of venom. Similarly administration of corticosteroids is not useful. Suction devices cannot extract venom injected under pressure.
Management during transportation to the hospital:

The presence of any local manifestation indicates grade 1 envenomation and requires hospitalization. Placement of an intravenous line is a necessary precaution to allow immediate vascular filling by macromolecules in case of arterial hypotension. Analgesics should be administered to patients in case of severe pain.
Management at the hospital:

- Envenomation grading.
- Laboratory testing (hemogram, hemostasis, kidney).

- Grade 0, a 4-hour observation may be proposed.
- Grade 1, hospitalization at least 24 hours.
- Grade 2 or 3, = antivenom.
At the hospital (2):

- Quantities of antivenom: pediatric dosage of antivenom is the same as in adults (only the volume of saline used to dilute the antivenom changes).
- Prompt use of antivenom is recommended for pregnant women (toxicity for the placenta).
- Preventing the life-threatening effects of envenomation takes priority over the risk of an anaphylactic reaction always manageable in a properly-equipped hospital setting.
- Infection after snakebite, regardless of clinical envenomation grade, is a slight but non-negligible risk. No consensus on the need for systematic antibacterial therapy.
- The role of surgery is limited and currently subject to controversy.
CONCLUSION:

Viper bites are at the origin of relatively rare medical emergencies in Europe, but systemic poisonings with life-threatening complications are possible. Important heterogeneity in the use of specific antivenoms due to the variable antidotes availability in the different European countries. As immunotherapy with infusion by intravenous route of purified antibody fragments is now considered as efficient and safe, antivenom treatment should be proposed to treat all moderate to severe European viper envenomation.
Review

Epidemiology of snakebites in Europe: A systematic review of the literature

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Management of snakebites in France

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