Case report

European viper envenomation recorded by French poison control centers: A clinical assessment and management study

V. Jollivet a, J.F. Hamel b, L. de Haro c, M. Labadie d, J.M. Saporie e, L. Cordier f, A. Villa g, P. Nisse h, E. Puskarczyk i, L. Berthelon j, P. Harry a, D. Boels a,*

a Poison Control Center, Angers University Hospital, France
b Clinical Research Center, Angers University Hospital, France
c Poison Control Center, Marseille University Hospital, France
d Poison Control Center, Bordeaux University Hospital, France
e Poison Control Center, Lyon University Hospital, France
f Poison Control Center, Toulouse University Hospital, France
g Poison Control Center, Paris University Hospital, France
h Poison Control Center, Lille University Hospital, France
i Poison Control Center, Nancy University Hospital, France
j Poison Control Center, Strasbourg University Hospital, France

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Abstract

Introduction: Immunotherapy is the gold standard treatment for patients bitten by European vipers in France; it significantly decreases morbidity, frequency and severity of complications and length of stay. A national prospective study was performed by all Poison Control Centers (PCC) to validate the emergency protocol for viper envenomations.

Methods: This prospective study included all cases of viper bites in France, treated or not with Viperfav® in 2013.

Results: In 2013, 277 cases of viper bites were collected: ratio M/F 2.1; mean aged 43 years (<15 years 25% 15-65 63% > 65 12%). The final severity was divided into 68 grades 0, 58 grades I, 62 grades IIA, 71 grades IIB and 18 grades III. One death was reported. Five patients had neurological signs. For the 114 patients who received Viperfav®, all systemic signs disappeared in 5 h and in 24 h for biological and neurological signs. No severe anaphylactic reaction with Viperfav® was reported. Late Viperfav® administration increased the risk of functional impairment 15 days after the bite (OR = 3.21 p = 0.043).

The administration of Low Molecular Weight Heparin (LMWH) increased the frequency of functional impairment to 15 days after the bite (OR = 6.38 p = 0.064), although Viperfav® was given in the first 18 h.

Discussion: This study confirms the efficiency, safety and recommendation of an early administration of a single dose of Viperfav®, LMWH should not be used. It also shows the extension of neurotoxic venom of vipers in France.

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1. Introduction

In France, adult and pediatric emergency cases of viper envenomation are relatively common due to the two main viper species in the country: Vipera aspis and Vipera berus (Bauchot R, 2005; de Haro L, 2012; Orsini P et al., 1998; Chippaux J.P, 2011). Other species (Vipera ursinii, Vipera seoanei, Vipera ammodytes) are seldom implicated.

In France, some authors have evaluated the incidence of viper bites at 100 to 1000 cases per year (de Haro L, 2012; Camou F et al., 2009). Emergency support services are very heterogeneous due to the lack of guidelines (Monteiro FNP et al., 2012; Malina T et al., 2013; Marano M et al., 2014). Advice from a clinical toxicologist at a Poison Control Centre (PCC) should be taken into account when determining the appropriate management and follow-up of patients bitten by vipers.

Clinical manifestations of European viper envenomations are currently well described (Audebert F et al., 1992; de Haro L et al.,...
Viperfav envenomations.

1999; Karlson-Stiber C et al., 2009).

Neurotoxins in the venom of some asp vipers can cause a disturbance of cranial nerves. Neurotoxins with a phospholipase A2 (PLA2) activity have been found in some viper venoms causing paralysis by affecting the neuromuscular transmission at either pre- or post-synaptic levels; these PLA2 neurotoxins do not cross the blood–brain barrier (Lewis and Gutmann, 2004; Lonati D et al., 2014).

Deaths due to viper envenomation are very rare (de Haro L, 2012). Only one death has been reported in our study.

A clinical grading of viper envenomation was established in 1992 by Audebert et al. (Reid HA, 1976; Audebert F et al., 1992; Audebert F et al., 1994). This classification was used to assess the severity of poisoning and its temporal patterns.

Because grade II was defined as a regional swelling associated or not with systemic signs or biological disturbances, a new classification was established in 2012 (Boels D et al., 2012) to divide grade II into grade IIA and IIB. The clinico-biological classification currently sets the immunotherapy indication from grade II (extensive swelling > 4 cm and/or systemic signs and/or neurological signs).

Immunotherapy with Viperfav® is now the gold standard treatment for patients bitten by European vipers in France (Boels D et al., 2012). Viperfav® contains purified F(ab′)2 fragments of equine antibodies, neutralizes venoms of three viper species (V. berus, aspis and ammodytes) (Anonymous, 2012). Some studies have evaluated the efficiency of immunotherapy and other symptomatic treatments (Boels D et al., 2012; de Haro L et al., 1998; Harry P et al., 1999; Karlson-Stiber C et al., 2009).

In order to improve hospital management of envenomed patients, we performed a prospective study to assess the epidemiology and clinical signs (with neurological signs) of viper envenomations.

This study validates the recommendations proposed by the PCC for viper bites management, especially in the assessment of Viperfav® (its efficiency and tolerance) and other treatments (antibiotics, corticosteroids and heparin).

2. Methods

A prospective case study of viper envenomations in France, in 2013, was carried out at the PCC.

Data related to calls to the PCC were extracted from the Poison Center database authorized by the French National Data Processing Committee (Accreditation no 747735). Protocol assistance support was given to all French PCC and ER.

We recorded all cases of patients bitten by an European viper (presence of typical fang marks and recognition of the snake, patient’s history). All personal patient data were made anonymous before their records were studied. A data collection form was completed by one clinical toxicologist and reviewed by another one. Given that this was a purely prospective and non-interventional study, and in accordance to French law, the local Ethics Committee waived the need to approve this study.

The patients were divided into three age groups: <15 years; 15–65 years and >65 years. The gender, severity of envenomation, time between the viper bite and Viperfav® administration, doses of Viperfav® and symptomatic treatments administrated, such as antibiotics, corticosteroids and low molecular weight heparin (LMWH), were also evaluated.

The only immunotherapy used was Viperfav®. A 4 mL vial of Viperfav® containing 396–468 mg of F(ab′)2 neutralizes 500 LD50 of V. berus venom and 1000 LD50 of V. aspis or V. ammodytes venoms. Viperfav® contains heterologous proteins and must be used under medical supervision in a hospital setting.

The symptoms of the viper bite were collected. The envenomation severity was based on the Boels et al. clinical and biological severity grading, ranging from grade 0 (white snap without envenomation), 1 (minimal envenomation), IIA and IIB (moderate envenomations) to III (severe envenomation). The grades were reassessed throughout the hospitalization period. The highest graduation was selected as the final grade (Boels D et al., 2012) (Table 1).

Each patient received clinical (systemic signs, neurological signs, swelling, haematoma, necrosis) and biological follow-up. The biological severity criteria were: leukocytes >15 000, platelets <150 000, Prothrombin time <60% and fibrinogen <2 g/L. Swelling levels were quantified in the following categories: local swelling, regional swelling (1: reaching hand/foot; 2: forearm/leg; 3: arm/thigh) and swelling reaching the trunk. The presence of localized haematoma around the bite site had to be considerable if it were to be retained as a criterion. The two fang marks located around the bite were frequently present and did not comply with our definition. These haematomas were either extensive around the fang marks, or diffused on the bitten limb in the form of bruises, pectechiae, purpura or haemorrhagic swelling. In our study, it was hard to precisely quantify all types of blood extravasation, and we preferred to limit our definition to the presence or absence of haematoma.

Clinico-biological monitoring was carried out during hospitalisation: admission, before the infusion and 5 h after Viperfav® infusion.

The time to the Viperfav® infusion was defined as the period between the viper bite and initiation of the infusion.

Each patient with grade I, II and III, treated or not with Viperfav® has been clinically followed by a phone call 15 days after envenomation to assess the persistence of functional impairment or local signs and look for signs of serum sickness.

Functional impairment at day 15 was defined as involving problems in moving the bitten limb (difficulty in walking or grasping objects) that persisted for more than 15 days after the bite. A venous Doppler ultrasound of the limbs was performed if there was any suspicion of thrombosis in the bitten limb.

The independance of categorical variables was tested using Fisher’s exact test. We performed logistic regression to explain the severity of envenomation/haematoma/functional impairment, respectively by age group, gender, gradation, time elapsing before the Viperfav® infusion and other symptomatic treatments.

3. Results

In 2013, 277 European viper bite cases were recorded in France.

3.1. Epidemiology

According to the geographical distribution, viper bites were more common in western and southwestern areas (Fig. 1).

Bites occurred mainly in summer (Fig. 2). The envenomation severity was not influenced by the season (p = 0.742). A higher bite rate was recorded in the afternoon.

In most cases, viper was seen (164 cases) by the patient but the species was only identified in 13% of envenomation cases (36 cases), including 29 cases with V. aspis and 7 with V. berus.

The circumstances of the bites were mostly accidental (91.7%):
encounters in nature (197 patients) or during gardening activities (57 patients). The second frequently encountered circumstance was when people handled the snake (8.3%). Out of the 277 cases, 17 cases were work-related accidents.

3.2. Population

A description of the general characteristics of the population is presented in Table 2.

The final severity was: 68 grades 0, 58 grades I, 62 grades IIa, 71 grades IIb and 18 grades III. This study showed that envenomation mainly concerned male subjects, with a male/female ratio of 2.1.

The mean age was 43 years (<15 years 25%; 15–65 years 63%; >65 years 12%). Hundred and eight patients were hospitalized for less than 24 h, 149 patients were hospitalized between 24 and 48 h, while 20 patients were hospitalized for more than 2 days, 2 grades

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### Table 1
Clinical gradation of viper envenomings, Boels et al. (2012).

<table>
<thead>
<tr>
<th>Grade</th>
<th>Envenomation</th>
<th>Clinical features</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No envenomation</td>
<td>Fang marks</td>
</tr>
<tr>
<td></td>
<td>White snap</td>
<td>No oedema</td>
</tr>
<tr>
<td>1</td>
<td>Minimal envenomation</td>
<td>Local oedema around the site of bite</td>
</tr>
<tr>
<td>2</td>
<td>Moderate envenomation</td>
<td>2a Regional oedema (most of the bitten limb) and/or haematoma</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2b Grade 2a + moderate general symptoms: mild hypotension, vomiting, diarrhoea, neurotoxic signs and/or biological criteria for severity:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Platelets &lt; 150 G/L</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Leukocytes &gt;15 G/L</td>
</tr>
<tr>
<td></td>
<td></td>
<td>INR &gt; 1.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fibrinogen &lt; 2 g/L</td>
</tr>
<tr>
<td>3</td>
<td>Severe envenomation</td>
<td>Extensive oedema spreading to the trunk and/or Severe general symptoms (severe hypotension &lt; 80 mmHg systolic, shock, bleeding)</td>
</tr>
</tbody>
</table>

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Fig. 1. Geographical distribution of viper bites in France in 2013.

Fig. 2. Seasonal distribution of viper bites in 2013 in France.
Table 2
Description of the patient population (total 277 patients) in France in 2013.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mode</th>
<th>Population n = 277</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>Male</td>
<td>186</td>
<td>67.15</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>90</td>
<td>32.49</td>
</tr>
<tr>
<td></td>
<td>Unknown</td>
<td>1</td>
<td>0.36</td>
</tr>
<tr>
<td>Age (years)</td>
<td>&lt;15</td>
<td>70</td>
<td>25.27</td>
</tr>
<tr>
<td></td>
<td>15–65</td>
<td>174</td>
<td>62.82</td>
</tr>
<tr>
<td></td>
<td>&gt;65</td>
<td>33</td>
<td>11.91</td>
</tr>
<tr>
<td>Grade</td>
<td>Grade I</td>
<td>0</td>
<td>24.55</td>
</tr>
<tr>
<td></td>
<td>Grade II</td>
<td>I</td>
<td>20.94</td>
</tr>
<tr>
<td></td>
<td>Grade II</td>
<td>IA</td>
<td>22.38</td>
</tr>
<tr>
<td></td>
<td>Grade II</td>
<td>II</td>
<td>25.63</td>
</tr>
<tr>
<td></td>
<td>Grade III</td>
<td>III</td>
<td>6.50</td>
</tr>
<tr>
<td>Circumstance</td>
<td>Accidental</td>
<td>254</td>
<td>91.70</td>
</tr>
<tr>
<td></td>
<td>Manipulation</td>
<td>23</td>
<td>8.30</td>
</tr>
<tr>
<td>Duration of hospital stay</td>
<td>&lt;24 h</td>
<td>108</td>
<td>38.99</td>
</tr>
<tr>
<td></td>
<td>24–48 h</td>
<td>149</td>
<td>53.79</td>
</tr>
<tr>
<td></td>
<td>&gt;48 h</td>
<td>20</td>
<td>7.22</td>
</tr>
<tr>
<td>Viperfav®</td>
<td>Single dose</td>
<td>108</td>
<td>94.74</td>
</tr>
<tr>
<td></td>
<td>Multiple doses</td>
<td>6</td>
<td>5.26</td>
</tr>
<tr>
<td>LMWH</td>
<td>Yes</td>
<td>14</td>
<td>5.05</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>71</td>
<td>25.63</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>Yes</td>
<td>22</td>
<td>7.94</td>
</tr>
</tbody>
</table>

IIB and 18 grades III (Table 2).

In these series, no patients had severe sequelae through follow-up. Three grades I were lost to follow-up.

One death was reported before he could receive medical care. A 53 years old male herpetologist was bitten on the forearm by V. aspis during a demonstration in southern France in June 2013. He quickly showed signs of discomfort, with the onset of shock in less than 20 min. He died of cardiac arrest 50 min after the bite and could not be resuscitated. There was no autopsy.

The envenomation severity was not influenced by age (p = 0.456) or gender (p = 0.894). Hundred twenty five patients had a bite to the lower limb, while 145 patients had a bite to the upper limb. The envenomation was significantly more severe when the upper limb was bitten (p = 0.002).

The details of the clinical and biological findings are presented in Table 3.

Fourty-one grades IIA, 44 grades IIB and 17 grades III cases had extensive swelling.

A hundred and two patients showed systemic symptoms and/or biological criteria for severity before Viperfav® infusion: 53 patients had systemic symptoms, 19 had biological criteria for severity and 15 had systemic and biological signs.

Gastrointestinal symptoms were the most frequent (nausea, vomiting, diarrhoea, abdominal pain). Severe symptoms (anaphylactoid reaction, signs of shock, angio-oedema, dyspnea) were mainly observed in severe poisoning cases.

In this series, we observed 5 cases with neurological signs (3 cases in southwestern France and 2 cases in western France): 3 ptosis, 3 glosso-pharyngeal paralysis (with swallowing disorders and dysgeusia) and 1 dysphonia. 2 cases were the result of bites by V. aspis, while in the 3 other cases the species could not be identified. Four neurotoxicity cases occurred in summer and the last occurred in spring.

There were 3 cases of renal failure, which were all transient without supportive care. Vipers envenomations are associated with transient hypotension resulting in a relative hypovolemia leading sometimes to acute renal failure from functional origin. There is no organic damage.

A Doppler ultrasound of the bitten limb was performed to 9 patients, with venous thrombosis confirmed in one of these cases.

Of the 72 patients who had haematoma, 64 had this symptom before Viperfav® infusion. These haematomas were observed before Viperfav® infusion or during follow-up. Eleven patients had local necrosis around the fang marks.

Among the biological criteria for severity (Table 3), 12 patients had leucocytes >15 000, 17 patients had platelets <150 000 and 5 patients had fibrinogen g/L. No prothrombin time <60% was observed in these series. No clinical consequences were related to biological criteria for severity. Biological criteria spontaneously normalized within a few days to weeks.

There were no longer haematoma in grades IIA, IIB and III. The presence of haematoma was not related to age. The occurrence of...

Table 3
Clinical and biological signs according to the envenomation grade.

<table>
<thead>
<tr>
<th>Envenomation grades</th>
<th>Grade IIA</th>
<th>Grade IIB</th>
<th>Grade III</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Population n = 62</td>
<td>Population n = 71</td>
<td>Population n = 18</td>
</tr>
<tr>
<td>Extensive swelling</td>
<td>41</td>
<td>66.1</td>
<td>44</td>
</tr>
<tr>
<td>Cardiovascular signs</td>
<td>31</td>
<td>43.7</td>
<td>15</td>
</tr>
<tr>
<td>Gastrointestinal signs</td>
<td>12</td>
<td>16.9</td>
<td>4</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>1</td>
<td>1.4</td>
<td>2</td>
</tr>
<tr>
<td>Hypertension</td>
<td>4</td>
<td>5.6</td>
<td>1</td>
</tr>
<tr>
<td>Shock</td>
<td>4</td>
<td>22.2</td>
<td></td>
</tr>
<tr>
<td>Respiratory signs</td>
<td>2</td>
<td>11.1</td>
<td></td>
</tr>
<tr>
<td>Dyspnea</td>
<td>1</td>
<td>1.4</td>
<td></td>
</tr>
<tr>
<td>Neurological signs</td>
<td>1</td>
<td>1.4</td>
<td></td>
</tr>
<tr>
<td>Moderate anaphylactoid reactions</td>
<td>4</td>
<td>5.6</td>
<td></td>
</tr>
<tr>
<td>Skin rash</td>
<td>4</td>
<td>5.6</td>
<td></td>
</tr>
<tr>
<td>Angio-oedema</td>
<td>3</td>
<td>16.7</td>
<td></td>
</tr>
<tr>
<td>Bronchospasm</td>
<td>1</td>
<td>1.4</td>
<td></td>
</tr>
<tr>
<td>Biological signs</td>
<td>9</td>
<td>12.7</td>
<td>14</td>
</tr>
<tr>
<td>Leukocytes &lt; 15 000</td>
<td>4</td>
<td>5.6</td>
<td></td>
</tr>
<tr>
<td>Prothrombin time &lt;60%</td>
<td>3</td>
<td>16.7</td>
<td></td>
</tr>
</tbody>
</table>

Note: the general symptoms included asthenia and malaise. The gastrointestinal symptoms included nausea, vomiting, diarrhoea and abdominal pain. The neurological signs included ptosis, glosso-pharyngeal paralysis and dysphonia.
haematoma was significantly more frequent among women (OR 3.663; \( p = 0.016 \)).

Thirty eight patients experienced persistent functional impairment 15 days after the bite. There was no more functional impairment in young patients under 15 years.

3.3. Immunotherapy

Of the 151 patients who needed treatment (62 grades IIA, 71 grades IIB and 18 grades III), 114 patients received immunotherapy (1 grade I, 43 grades IIA, 53 grades IIB and 17 grades III): 75.5%. The grade I patient received Viperfav® without PCC advice. The time between the bite and the Viperfav® infusion was spread between 30 min and 73 h.

Six patients received 2 doses of Viperfav® without PCC advice. Of the 114 patients treated with Viperfav®, 102 had extensive swelling (36 regional swelling type 1, 45 regional swelling type 2, 14 regional swelling type 3 and 7 trunk swelling) before infusion. Clinical reassessment showed increased swelling in 9 cases. Type 1 regional swelling increased to type 2, and type 2 regional swelling increased to type 3. The average Viperfav® infusion time was 6.7 h for these 9 patients.

All moderate and severe systemic signs regressed after a single Viperfav® infusion.

Gastrointestinal, cardiovascular, respiratory and allergic signs regressed 5 h after immunotherapy. A case of glosso-pharyngeal paralysis lasted 15 h in a grade IIB patient who had been infused 2.5 h after the bite. One case of ptosis lasted less than 24 h with a grade IIB patient who had received a dose of Viperfav® 22 h after the bite. Shocks were resolved within 5 h after the beginning of Viperfav® infusion.

Haematoma was significantly more frequent when the Viperfav® infusion was performed more than 18 h after the bite (OR 2.973; \( p = 0.034 \)). Functional impairment was significantly more frequent when the Viperfav® infusion was performed more than 18 h after the bite (OR 3.208; \( p = 0.043 \)).

All biological criteria for severity were normalized in 34 patients. For 9 of them, normalization occurred within hours after Viperfav® infusion.

3.4. Adverse reaction to Viperfav®

No cases of severe anaphylactic reactions were reported after Viperfav® infusion. Viperfav® was deemed to be safe, only one patient experienced intolerance after infusion (conjunctivitis with conjunctival erythema and pruritus). His symptoms spontaneously resolved after infusion. Only one subject presented symptoms compatible with serum sickness (polyarthralgia, asthenia, myalgia, inflammatory syndrome with elevated sedimentation rate). His symptoms favourably progressed with anti-histamines. He had received one dose of Viperfav® and antibiotics.

3.5. Other treatments

Seventy-one patients received antibiotics preventively (Table 2). Only two patients in this series had local infection around the fang marks.

Twenty-two patients received corticosteroids during their hospital stay (Table 2). There was no more functional impairment in patients who received corticosteroids.

Fourteen patients were preventively treated with LMWH. The administration of LMWH increased the frequency of functional impairment to 15 days after the bite (OR = 6.38 \( p = 0.064 \)), even though Viperfav® was given in the first 18 h.

Nineteen patients had a tetanus booster shot. No tetanus cases were reported in this series.

4. Discussion

4.1. Epidemiology

Although viper envenomations are common in France, there is only few epidemiological data in the literature which are only estimates. Our study identified 277 cases of viper bites in France in 2013 by PCC. These findings probably underestimate the annual incidence.

More bites were reported south of the Loire but also in the western regions, which is consistent with the geographical distribution of vipers. However, cases with other species remain possible in the South of the France.

As it is difficult for patients to differentiate snakes, only 36 among the 164 snakes seen were identified. The species most often identified were V. aspis and V. berus, with a predominance of V. aspis (29 cases).

This study confirmed the extension of the range of V. aspis, with neurotoxic venom, in western France, although previously described only in the south of France (Guiavarch et al., 2011; Jan V et al., 2002; de Haro L et al., 2002).

Envenomations occur in warmer seasons, especially summer, as described in previous studies (de Haro et al., 2009; Petite J, 2005). Vipers come out of hibernation in the spring and people are often outside in hot seasons (Chippaux JP, 2011). Bites in winter are generally related to accidental manipulation of the animal (lifting a tarp, pick up a pile of wood ...).

The bites reported here were mainly accidental, but some envenomations due to voluntary snake manipulation could be avoided.

4.2. Clinical

Among the 277 patients, only 18 grades III cases (6.5%) were recorded thanks to widespread use of immunotherapy. The severity of envenomation was not higher in patients with extreme ages. A prospective study of moderate to severe viper envenomations (\( n = 268 \)) conducted by French PCC between 1999 and 2009 revealed no difference in the distribution of severity in different age groups, including extreme ages and confirmed the benefit of this treatment (Boels et al., 2012).

Upper limbs were bitten during gardening or handling, whereas lower limbs were bitten during accidental encounters.

Concerning systemic signs, gastrointestinal symptoms were predominant. Peripheral ischemia was not reported in this series. These data confirmed that fasciotomy is unnecessary for viper envenomations in France (de Haro L et al., 2009). In our study, haematoma was significantly more frequent among women.

Only 4 shocks were identified in this series, while the rate was around 27% for grades II and III for several years (Harry P et al., 1999).

One death was reported before he could receive medical care. This rapid death could be explained by an anaphylactic reaction or intravascular bite. Given the clinical expression the most likely hypothesis is intravascular bite.

In this prospective study, the search for neurological signs was systematic.

Five cases of neurotoxicity due to V. aspis were highlighted. The symptoms due to viper venom containing neurotoxic PLA2 components were the same as those described in previous studies (de Haro L, 2012; Garrigues T et al., 2005; Ferquel E et al., 2007; Lonati D et al., 2014): ptosis, glosso-pharyngeal paralysis and
dysphonia. Some authors explained that neurotoxic effects were inconsistently observed due to variability in factors, such as different amounts of venom injected, concentration of PLA2 component, environmental factors and individual susceptibility (Lonati D et al., 2014). Although one case of neurotoxicity with V. berus was recently published, envenomation by V. berus with neurological signs remains very limited (Malina T et al., 2013).

4.3. Immunotherapy and medical care

Only 20 patients (7.22%) were hospitalized for over 48 h thanks to enhanced care and to the protocol assistance given to all ER and PCC.

Several recent studies have been carried out in Europe and have allowed the development of specific treatments and protocols for the management of envenomated victims (Boels D et al., 2012; de Haro L et al., 2009).

Immunotherapy with F(ab)2 fragments is currently the gold standard treatment for patients bitten by European vipers in France (Boels D et al., 2012; de Haro L et al., 1998; Harry P et al., 1999; Malina T et al., 2013; Harry P & de Haro L., 2002).

In our series, of the 151 envenomations that required immunotherapy, 37 patients did not received Viperfav®. Several explanations can justify this lack of treatment: patients came late to ER or to their general practitioner. Some emergency physicians decided not to infuse Viperfav® as they were unfamiliar with this practice. PCC were not contacted or were called late. Emergency monitoring periods were too short (<6 h).

Moreover, six patients received 2 doses of Viperfav® without PCC advice.

Immunotherapy reduces swelling extension (Karlson-Stiber & Persson, 1994; Karlson-Stiber C et al., 1997). Of the 114 patients who received Viperfav®, 92.1% had no swelling extension after infusion and all systemic symptoms had disappeared within 5 h of infusion immunotherapy. In contrast, biological criteria for severity as well as neurological symptoms seemed slower to normalize (Guiavarch M et al., 2011; Karlson-Stiber C et al., 2009). They eventually disappeared within 24 h after the bite in our study.

Some authors demonstrated that a single dose of Viperfav® led to the disappearance of systemic signs at the end of the infusion period, including patients in shock, and hemostasis disorders were corrected within 6–8 h (n = 62 patients) (Boels D et al., 2012). Our series also confirmed the effectiveness of a single dose of Viperfav®. Multiple doses did not show additional benefits (swelling, systemic and biological signs) and increased care cost.

Previous studies had shown that Viperfav® had to be early administered to improve the efficiency (Camou F et al., 2009; Chippaux JP, 2011; Boels D et al., 2012; Bentur et al., 1997). To be effective, immunotherapy should be administered within the first 10 h after the bite, according to the French 2012 article (Boels D et al., 2012). Under these conditions, Viperfav® therapy can reduce the length of the hospital stay threefold, the risk of haematoma and by a factor three functional impairment.

Our data confirmed that Viperfav® should be infused as early as possible when indicated (grades II A, IIB and III) in order to reduce the incidence of haematoma and functional impairment at 15 days (Boels D et al., 2012).

Concerning other symptomatic treatments, our data showed that LMWH increased functional impairment when patients had received early Viperfav® treatment.

Previous studies showed that LMWH increased haematoma risk and worsened functional impairment (Boels D et al., 2012) and other authors have also issued warnings regarding high dose intravenous heparin therapy because of the obvious risk of aggravating bleeding into the tissues (Karlson-Stiber & Persson, 1994).

We do not advise the preventive use of LMWH in case of envenomation by an European viper. In the literature, deep venous thrombosis has often been suspected, but seldom confirmed (Karlson-Stiber & Persson, 1994). Corticosteroids and antibiotics have no benefits regarding the duration of hospital stay and functional impairment, a previous study consolidated this data and did not recommended them (Boels D et al., 2012). Antibiotics should not be routinely given, but prompt treatment is necessary when an infection is suspected (Boels D et al., 2012). Corticosteroids do not act on the swelling which is due to a capillary leak rather than inflammation and they increase the risk of bacterial infection (Boels D et al., 2012; Karlson-Stiber & Persson, 1994; Karlson-Stiber C et al., 2006).

4.4. Adverse reaction to Viperfav®

This study also confirmed previous reports concerning the safe use of Viperfav® (de Haro L et al., 1998; Harry P et al., 1999; de Haro L et al., 2009). No cases of severe anaphylactoid reactions were observed.

Cases of serum sickness after immunotherapy are very uncommon in the literature (Boyer LV et al., 2013; Karlson-Stiber & Persson, 1994). One case has been identified in our study.

4.5. Limitations

The primary limitations of this study were those inherent to the use of prospective data and PCC records. Information were collected over the phone and recorded by a specialist from the Poison Center. Patient records from the Emergency Departments could not be reviewed in some cases, and we only had access to PCC data. Although PCC clinical toxicologist propose recommendations, final decisions to treat patients with one or more doses of Viperfav®, or to initiate other symptomatic treatments (corticosteroids, antibiotics, LMWH), were taken by the emergency physician.

5. Conclusion

This study allowed homogeneous and appropriate management cares in viper envenomation in France. PCC unified their guidelines. This series highlighted the extension of the range of V. aspis with neurotoxic venom in western France, although previously described in the South of France only. This study also confirms the efficiency and tolerance of a single dose of Viperfav®, It also consolidates the conclusions of previous studies whereby it was advised that Viperfav® infusion had to be initiated as early as possible and also that LMWH therapy was not recommended. The routine use of antibiotics and corticosteroids do not seem to improve functional impairment nor the duration of hospital stay. Short hospital stays are thanks to improved prognosis, thus lowering the total cost of treatment. In these series, advice from a clinical toxicologist from a Poison Control Center to determine the most appropriate management and follow-up for patients bitten by a viper was very important.

The study is ongoing in 2014 to consolidate treatments and achieve a national consensus on therapeutic management regarding viper envenomation. Advice from a clinical toxicologist from a PCC should be taken into account when determining the appropriate management and follow-up of patients bitten by a viper.

Conflict of interest

All authors declare that there are no conflicts of interest.
Role of funding source

Nothing declared.

Contributors

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