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Virginie JOLLIVET

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ABREVIATIONS

LMWH: Low Molecular Weight Heparin

OR: Odd Ratio

PCC: Poison Control Center

PLAN

INTRODUCTION

In France, adult and pediatric emergency cases of viper envenomation are relatively common due to the two main viper species in the country: the asp viper (*Vipera aspis*) and the adder viper (*Vipera berus*) (Bauchot R, 2005; de Haro L, 2012; Orsini P et al, 1998; Camou F et al, 2009; Chippaux JP, 2011). Other vipers (*Vipera ursinii*, *Vipera seoanei*) are seldom implicated.

In France, some authors have evaluated the incidence of viper bites at 100 to 1000 cases per year (de Haro, 2012; Camou F, 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 envenomation are currently well described (Boels D et al, 2012): pain and local swelling in the event of minor envenomation; limb swelling, systemic symptoms and biological disorders in cases of moderate envenomation; and extensive swelling spreading to the trunk and/or acute systemic symptoms in severe envenomations (de Haro L et al, 1998; Harry P et al, 1999). Neurological symptoms have been reported in the South of France (de Haro L, 2012; de Haro L et al, 2009; de Haro et al, 2002). Neurotoxins in the venom of some asp vipers can cause a disturbance of cranial nerves.

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 abnormalities, a new classification was established in 2012 (Boels D et al, 2012) to divide grade II into grade IIA and IIB (Annex 1). The clinico-biological classification currently sets the immunotherapy indication from grade II (extensive swelling > 4cm and/or systemic signs and/or neurological signs).

Immunotherapy with Viperfav® is now the gold standard treatment for patients bitten by European vipers (Boels D et al, 2012). Viperfav® contains purified F(ab')2 fragments of equine antibodies, neutralizes venoms of three viper species (Vipera berus, aspis and ammodytes). 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 with the assessment of Viperfav® (its efficiency and tolerance) and other treatments (antibiotics, corticosteroids and heparin).

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 n°747735). Protocol assistance support was given to all French PCCs and emergencies (Annex 1).
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 rendered anonymous before their records were studied. A data collection form (Annex 2) was completed by one clinical toxicologist and reviewed by another one. Given that this was a purely prospective and non-interventional study, and according 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. Gender, the severity of envenomation, the time between the viper bite and Viperfav® administration, the 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 4mL vial of Viperfav® containing 396-468mg of F(ab')2 neutralizes 500 LD50 of *Vipera berus* venom and 1000 LD50 of *Vipera aspis* or *Vipera 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 as grade 0 (white snap without envenomation), I (minimal envenomation), IIA and IIB (moderate envenomations), III (severe envenomation). The grades were reassessed throughout the hospitalization period. The highest gradation was selected for the final grade.
Each patient received clinical (systemic signs, neurological signs, swelling, haematoma, necrosis) and biological follow up. The biological severity criteria were: leukocytes > 15 000, thrombocytes < 150 000, TP < 60% and fibrinogen < 2g/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 was to be retained as a criterion. Simple red points located around the bite were frequently present and did not comply with our definition. These haematomas were either extensive around the fang marks, or diffuse on the bitten limb in the form of bruises, petechiae, 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 steady 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. The days of hospital stay were considered to run from hospital admission to hospital discharge.

Each patient with grade I, II and III, treated or not 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 scan of the limbs was performed if there was any suspicion of thrombosis.

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.

RESULTS

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

Epidemiology

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

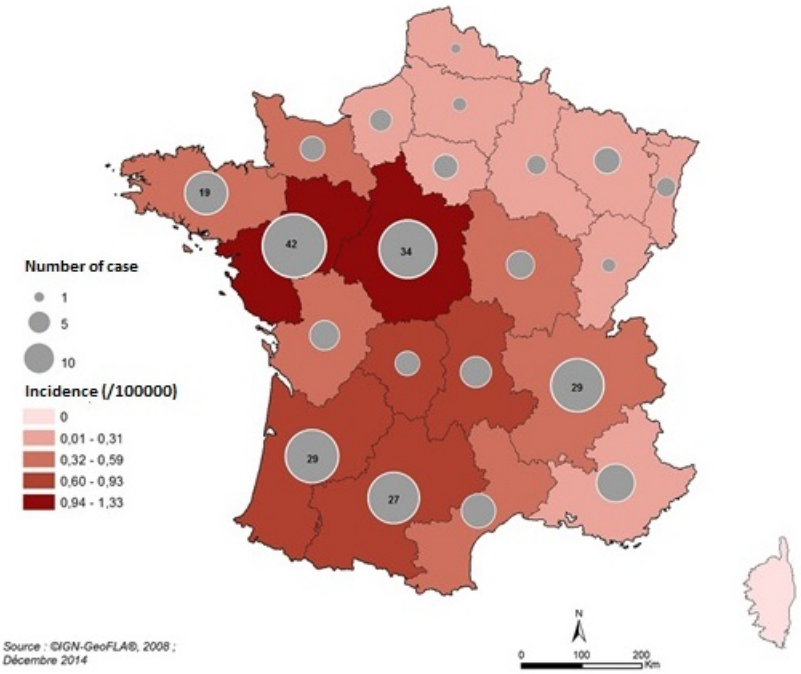
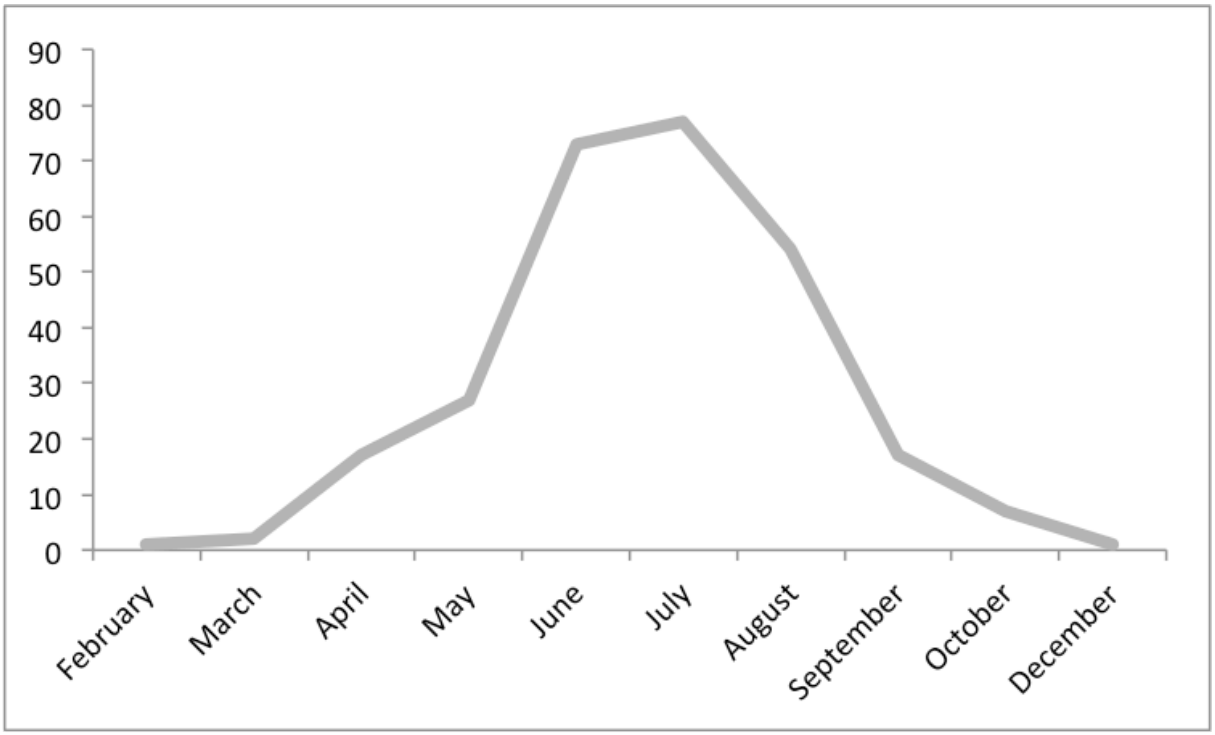


Figure 1 : Geographical distribution of viper bites in France in 2013.

Bites occurred mainly in summer (Graph I). The envenomation severity was not influenced by the season (p= 0,742). The prime time for bites was in the afternoon.

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



Graph I: Seasonal distribution of viper bites in 2013 in France.

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 occurred in a professional setting.

Population

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

Table I: Description of the patient population (total 277 patients) in France in 2013.

Variable	Mode	Population n= 277	Percentage
Gender	Male	186	67.15
	Female	90	32.49
	Unknow	1	0.36
Age (years)	<15	70	25.27
	15-65	174	62.82
	>65	33	11.91
Grade	0	68	24.55
	I	58	20.94
	IIA	62	22.38
	IIB	71	25.63
	III	18	6.50
Circumstance	Accidental	254	91.70
	Manipulation	23	8.30
Duration of hospital stay	<24h	108	38.99
	24-48h	149	53.79
	>48h	20	7.22
Viperfav	Single dose	108	94.74
	Multiple doses	6	5.26
HBPM	Yes	14	5.05
ATB	Yes	71	25.63
CTC	Yes	22	7.94

The final severity was: 68 grade 0, 58 grades I, 62 grades IIA, 71 grade IIB and 18 grade III. This study showed that envenomation mainly concerned male subjects, with a male/female ratio of 2.1. The average 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 grade IIB and 18 grade III (Table I).

In this series, no patients had sequelae at follow up.

One death was reported before he could receive medical care.

A 53 year old male herpetologist was bitten on the forearm by *Vipera 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.

Table II: Multivariate analysis of the severity of envenomation in all patients bitten by a viper.

Grades : 0, 1 vs 2a, 2b, 3

	Odds Ratio	[95% Conf.	Interval]	P>z
Age (ref: 15-65 years)				
<15a	0.801	0.448	1.434	0.456
>65a	1.852	0.794	4.322	0.154
Gender : female	1.038	0.599	1.800	0.894
Locality : Upper limb(ref : Lower limb)	**2.349**	**1.381**	**3.995**	**0.002**
Season : ref: spring				
Summer	1.099	0.627	1.926	0.742
Fall - winter	0.599	0.195	1.837	0.370

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) (Table II).

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

Table III: Clinical and biological signs according to the envenomation grade.

	Envenomation grades					
	Grade IIA		Grade IIB		Grade III	
	Population n= 62	Percentage	Population n= 71	Percentage	Population n= 18	Percentage
Extensive swelling	41	66.1	44	62.0	17	94.4
General signs			15	21.1	8	44.4
Digestive signs			31	43.7	9	50.0
Cardiovascular signs						
Tachycardia			12	16.9	2	11.1
HTA			4	5.6		
Mild hypotension			6	8.45	8	44.4
Shock					4	22.2
Respiratory signs						
Dyspnea			1	1.4	2	11.1
Desaturation			1	1.4		
Neurological signs			4	5.6	1	5.6
Moderate anaphylactoid reactions						
Skin rash			4	5.6		
Angio-oedema			4	5.6	3	16.7
Bronchospasm			1	1.4		
Biological signs						
Leukocytes> 15 000			9	12.7	3	16.7
Thrombocytes< 150 000			14	19.7	3	16.7
TP < 60%						
Fibrinogen< 2 g/L			4	5.6	1	5.6

Note: the general symptoms included asthenia and malaise. The digestive symptoms included nausea, vomiting, diarrhea and abdominal pain. The neurological signs included ptosis, glosso-pharyngeal paralysis and dysphonia.

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

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

Digestive symptoms were the most frequent (nausea, vomiting, diarrhea, 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 dysgueusia) and 1 dysphonia. 2 cases were the result of bites by *Vipera 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.
A Doppler ultrasound of the bitten limb was performed in 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 III), 12 patients had leukocytes > 15 000, 17 patients had thrombocytes < 150 000 and 5 patients had fibrinogen < 2g/L. No TP < 60% was observed in this series. No clinical consequences were related to biological criteria for severity. Biological criteria spontaneously normalized within a few days to weeks.

A multivariate analysis of haematoma criteria is presented in Table IV.

Table IV: Haematoma. Multivariate analysis. France 2013.

Haematoma	Odds Ratio	[95% Conf.	Interval]	P>z
Time>= 18h	**2.972639**	**1.084797**	**8.145837**	**0.034**
Grades IIb and III (ref: IIa)	*2.230766*	*0.8737996*	*5.695034*	*0.093*
Gender = F	**3.662729**	**1.27917**	**10.48773**	**0.016**
Age				
<15y	1.389328	0.4651166	4.149994	0.556
>65y	0.5172073	0.1661064	1.610434	0.255

There were no longer haematoma in grades IIA, IIB and III. The presence of haematoma was not related to age. The occurrence of haematoma was significantly more frequent among women (OR 3.663; p=0.016).

A multivariate analysis of functional impairment criteria is presented in the Table V.

Table V: Functional impairment. Multivariate analysis. France 2013.

Functional impairment	OR	[95% Conf.	Interval]	P>z
Time>= 18h	**3.208**	**1.038**	**9.914**	**0.043**
Heparin if time<18h	***6.381***	***0.901***	***45.195***	***0.064***
Heparin if time >=18h	1.119	0.117	10.714	0.922
Age<15yrs	0.277	0.055	1.402	0.121
Corticosteroids	1.404	0.328	6.015	0.647

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

Immunotherapy

Of the 151 patients who needed treatment (62 grade IIA, 71 grade IIB and 18 grade III), 114 patients received immunotherapy (1 grade I, 43 grade IIA, 53 grade IIB and 17 grade III): 75.5%. The grade I patient received Viperfav® without PCC advice. The average Viperfav® infusion time was 11.7 h. Infusion delays ranged from 30 min to 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 hours for these 9 patients.

All moderate and severe systemic signs regressed after a single Viperfav® infusion.
Digestive, 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. And one case of ptosis lasted less than 24 h in 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) (Table IV).

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) (Table V).

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

Tolerance

No 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 favorably progressed with anti-histamines. He had received one dose of Viperfav® and antibiotics.

Other treatments

Seventy-one patients received antibiotics preventively (Table I). Only two patients in this series had local infection around the fang marks.
Twenty-two patients received corticosteroids during their hospital stay. There was no more functional impairment in patients who received corticosteroids (Table III).
Thirteen patients were preventively treated with LMWH. Patients who received heparin therapy were more likely to have remote functional impairment if Viperfav® infusion was performed within 18 h after the bite (OR 6.381; p=0.064) (Table V). Nineteen patients had a tetanus booster shot. No tetanus cases were reported in this series.

DISCUSSION

Epidemiology

Although viper envenomations are common in France, there is only few epidemiological data in the literature, soonly rough estimates are possible. 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.
As it is difficult for patients to differentiate snakes, only 36 among the 164 snakes seen were identified. The species most often identified were *Vipera aspis* and *Vipera berus*, with a predominance of *Vipera aspis* (29 cases).
This study confirmed the extension of the range of *Vipera 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 volontary snake manipulation could be avoided.

Clinical

Among the 277 patients, only 18 grade 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) monitored 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 value of this treatment (Boels D et al, 2012). Our study reconfirmed these findings.

Both the upper and lower limbs were frequently bitten. Upper limbs were bitten during gardening or handling, whereas lower limbs were bitten during accidental encounters.

Concerning systemic signs, digestive symptoms were predominant. The 3 cases of transient renal failure were not due to a toxic mechanism but rather to acute functional renal failure. 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).

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

Five cases of neurotoxicity 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 *Vipera berus* was recently published, envenomation by *Vipera berus* with neurological signs remain very limited (Malina T et al, 2013). There were no cases reported in our series.

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 emergencies 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 (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; Boyer LV et al, 2013).

In our series, of the 151 envenomations that required immunotherapy, 114 patients were treated with Viperfav®. After being bitten, 37 patients would receive the Viperfav®. Several explanations can justify this lack of treatment: patients came late at emergencies or in their general practitioner. Some emergency physicians decided not to infuse Viperfav® as they were unfamiliar with this practice. PCCs 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 C et al, 1994; Harry P, 2000; Karlson-Stiber C et al, 1997). Of the 114 patients who received Viperfav®, 92.1% had no swelling extension after infusion. 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 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 to 8 h (n= 62 patients) (Boels D et al, 2012). Our series also confirmed the effectiveness of a single dose of Viperfav®. Multiple doses had no additional benefits (swelling, systemic and biological signs) and increased care cost.

Previous studies had shown that Viperfav® had to be administered precociously to improve the efficiency (Camou F et al, 2009, Chippaux JP, 2011; Boels D et al, 2012; Bentur Y, 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 by threefold and 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 IIA, IIB and III) in order to reduce the incidence of haematoma and functional impairment in 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). We do not advise the preventive use of LMWH in case of envenomation by an European viper. 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 C et al, 1994). In the literature, deep venous thrombosis has often been suspected, but seldom confirmed (Karlson-Stiber C et al, 1994).
Concerning the benefits of prophylactic antibiotherapy, we observed no systemic infections with or without antibiotic treatment in our series. Antibiotics should not be routinely given, but prompt treatment is necessary only if infection is suspected (Boels D et al, 2012).

Corticosteroids and antibiotics have no benefits regarding the duration of hospital stay and functional impairment, so they are not recommended for routine treatment of viper envenomation cases in Europe (Boels D et al, 2012). Corticosteroids do not act on swelling due to a capillary leak rather than inflammation and they increase the risk of bacterial infection (Boels D et al, 2012; Karlson-Stiber C et al, 1994; Karlson-Stiber C et al, 2006).
No tetanus cases have been reported following snakebite in Europe, including in this study. We recommend checking the immunization status and giving booster shots if necessary.

Tolerance

This study also confirmed previous reports concerning the safety of Viperfav® (de Haro L et al, 1998; Harry P et al, 1999; de Haro L et al, 2009). No cases of anaphylactoid reactions were identified after infusion. Only one case of intolerance was observed with allergy symptoms (conjunctival erythema and pruritus).

A case of serum sickness was reported while the patient received a dose of Viperfav and antibiotics. His symptoms favorably progressed with anti-histamines. Cases of serum sickness after immunotherapy are very uncommon in the literature (Boyer LV et al, 2013; Karlson-Stiber C et al, 1994).

Limitations

The primary limitations of this study were those inherent to the use of prospective data and PCC records. Information was collected over the phone and recorded by a specialist in 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 PCCs 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.

CONCLUSION

This study allowed homogenous and appropriate management cares in viper envenomation in France. PCC unified their recommendations. This series highlighted the extension of the range of *Vipera aspis* with neurotoxic venom in western France, although previously described in the South of France. This study also confirmed the efficiency and tolerance of a single dose of Viperfav®. It also confirmed the conclusions of previous studies where by it was advised that Viperfav® infusion be initiated as early as possible and LMWH therapy was not advised. The routine use of antibiotics and corticosteroids did not seem to improve functional impairment or the duration of hospital stay. Short hospital stays were due to improved prognosis, thus lowering the total cost of treatment. In this series, advice from a clinical toxicologist at a Poison 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 at a PCC should be taken into account when determining the appropriate management and follow-up of patients bitten by a viper.

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PROTOCOLE POUR LA PRISE EN CHARGE DES ENVENIMATIONS VIPERINES
(Vipères de France)

Objectif : Ce protocole national des Centres antipoison français en partenariat avec les services d'Urgences a pour objectif de mieux cerner l'épidémiologie et la clinique (gravité, signes neurologiques éventuels…) des envenimations vipérines en France ainsi que l'efficacité et la tolérance du Viperfav®. Le but sera in-fine de valider des recommandations nationales des CAPTV de prise en charge des morsures vipérines dans les services d'Urgences.

Merci de notifier toutes les suspicions "raisonnables" de morsure de vipère (y compris les "morsures blanches-grade 0), que les patients soient traités ou non par Viperfav au Centre Antipoison d'Angers
TEL : 02 41 48 21 21

RAPPEL DE LA CONDUITE À TENIR POUR LA PRISE EN CHARGE DES ENVENIMATIONS VIPERINES

Description des couleuvres et vipères en France :

COULEUVRE	VIPERA BERUS	VIPERA ASPIS
Pupilles rondes	Pupilles en fente	Pupilles en fente
Queue effilée	Queue courte après le cloaque	Queue courte après le cloaque
1 seule rangée d'écailles labiales	2 rangées d'écailles labiales	3 rangées d'écailles labiales
9 grosses écailles sur la tête	3 grosses écailles sur la tête : 1 frontale et 2 pariétales	Petites écailles semblables sur la tête
2 écailles cloacales	Ecaille cloacale unique	Ecaille cloacale unique
Pas de crochet	Crochets rétractiles dans la gueule	Crochets rétractiles dans la gueule

GRADES D'ENVENIMATION	SYMPTOMES	TRAITEMENT
Grade 0	Aucun symptôme, marque des crochets.	Surveillance **6h** à l'hôpital.
Grade I	Œdème uniquement localisé au niveau de la morsure. Douleur modérée.	Ttt symptomatique. Surveillance **24h** à l'hôpital. Bilan bio toutes les 12h.
Grade IIA **Grade IIB**	Œdème extensif (autour du point de morsure sur plus de 4cm ou en cas de morsure digitale dès que l'œdème atteint la main ou le pied) Et/ou suffusion hématique au-delà des points de morsure Et/ou adénopathie satellite (axillaire ou inguinale) Et/ou douleur intense. Grade IIA + Signes généraux* Et/ou biologiques **	Administration unique de **VIPERFAV®** 1 dose de 4ml dans 125ml de sérum physiologique perfusée sur 1 heure, le plus précocement possible
Grade III	Extension de l'œdème au tronc Et/ou signes généraux sévères***	

***Signes généraux** : digestifs (vomissements, douleurs abdominales), cardio-vasculaires (hypotension, bradycardie), neurologiques (ptôsis, paires crâniennes), autres…

****Signes biologiques de gravité :**

- Leucocytes >15 000/mm^3
- Plaquettes < 150 000/mm^3
- TP < 60%
- Fibrinogène < 2 g/L

*****Signes généraux sévères :** réaction anaphylactoïde, choc, OAP, coagulopathie, insuffisance rénale.

CONDUITE À TENIR

⇨ Traitement symptomatique :

- Soins locaux simples (désinfection)
- Vérifier vaccination antitétanique
- Exceptionnellement si nécrose ou hématome local d'un doigt, avis chirurgical pour excision
- PAS de corticoïde, PAS d'anticoagulants (HBPM, HNF) (aggravent l'hématome et allongent la durée d'hospitalisation), PAS d'antibiotiques systématiques
- Surveillance horaire de l'extension de l'œdème vers un grade II.

⇨ Antalgiques : Palier 1 ou 2.

⇨ Viperfav® : indiqué dès le grade IIA.

- Le plus précoce possible pour une efficacité optimale, mais possible jusqu'à 72h après la morsure
- 1 seule dose et même posologie pour adultes/enfants/femmes enceintes
- Perfusion de 4ml dans 125ml de sérum physiologique sur 1 heure
- Dépister des signes d'intolérance immédiate au Viperfav®.

⇨ Surveillance clinico-biologique :

- Contrôle biologique avant administration de Viperfav® à la recherche des critères biologiques de gravité précédemment cités et contrôler 6 à 12h après administration du Viperfav®
- Rechercher les signes cliniques précédemment cités et particulièrement la présence de signes neurologiques et notifier leur éventuelle persistance après Viperfav®en précisant la durée.

⇨ Si suspicion de thrombose veineuse profonde du membre mordu :

Echo-doppler veineux et traitement de la thrombose veineuse profonde si nécessaire.

⇨ Suivi à J15 du patient: (assuré par le Centre Antipoison d'Angers)

Recherche de signes de maladie sérique

Recherche d'une gène fonctionnelle persistante.

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FICHE DE RECUEIL DES ENVENIMATIONS VIPERINES

A retourner au Centre Antipoison d'Angers – Fax : 02.41.35.55.07 - Centre-antipoison@chu-angers.fr

Dossier	
• CAP concerné :	• N° dossier CAP : .....

Patient

• Initiale : __ __ (1ères lettre nom et prénom)
• Sexe :
☐ féminin ☐ masculin
• Date de naissance : .....
• Poids : ..... kg

• Antécédents :

oui	non	
☐	☐	Antécédent de morsure
☐	☐	Allergie à Viperfav® ou sérums équins

Lister les traitements habituels : .....

Circonstances

- A vu le serpent : ☐ non ☐ oui - identification de l'espèce :
Date et heure de la morsure: / / N° département..... Accident de travail : O / N
Siège de la morsure : .....
Circonstances de la morsure : .....

	Date	Heure
Entrée à l'hôpital	___/___/_____	
Sortie définitive de l'hôpital	___/___/_____	

Conclusion: **Grade d'envenimation**: .....

CLINIQUE (à compléter)

	Symptômes	Date et heure d'apparition : .../.../... ...h...	Persistance 4h après Viperfav® (oui ou non)
Signes généraux	Fièvre		
	Asthénie		
	Malaise		
Signes digestifs	Nausées		
	Vomissements		
	Diarrhée		
	Douleurs abdominales		
Signes cardio-vasculaires	FC (bpm)		
	PA (mmHg)		
	Signes de choc		
Signes respiratoires	Dyspnée		
	OAP		
	Autres		
Signes neurologiques	Ptosis		
	Paralysie occulo-motrice		
	Paralysie glosso-pharyngée		
	Autres		
Réactions dues au venin	Eruption cutanée		
	Œdème de Quincke		
	Bronchospasme		
	Choc anaphylactoïde		
Autres	Préciser		

	Symptômes	PEC initiale : .../.../... ....h.....	Avant Viperfav® .../.../... ...h...	Réévaluation (6h après Viperfav®)
Signes locaux	**Douleur** (1 faible, 2 modérée, 3 fort)	1☐ 2☐ 3☐	1☐ 2☐ 3☐	1☐ 2☐ 3☐
	Œdème local	oui ☐ non ☐	oui ☐ non ☐	oui ☐ non ☐
	Œdème régional 1= main ou pied 2= avant bras ou jambe 3= bras ou cuisse	1☐ 2☐ 3☐	1☐ 2☐ 3☐	1☐ 2☐ 3☐
	Œdème atteignant le tronc	Localisation:	Localisation:	Localisation:
	Hématome* 1= main ou pied 2= avant bras ou jambe 3= bras ou cuisse	1☐ 2☐ 3☐	1☐ 2☐ 3☐	1☐ 2☐ 3☐
	Nécrose	oui ☐ non ☐	oui ☐ non ☐	oui ☐ non ☐
	Adénopathie satellite	oui ☐ non ☐	oui ☐ non ☐	oui ☐ non ☐

* Hématome = collection hématique, suffusions hématiques, pétéchies...

BIOLOGIE

	Résultats du bilan biologique				
	PEC initiale .../.../.. ..h..	**Prélèvement avant Viperfav® (<6h)** .../.../... ...h...	**Prélèvement 6-12h après Viperfav®** .../.../... ...h...	**Suivis éventuels** .../.../... ...h...	.../.../... ...h...
Leucocytes					
Plaquettes					
TP					
Fibrinogène					
Créatinine					

TRAITEMENTS EFFECTUES AUX URGENCES (détailler)

VIPERFAV®
Date et Heure de la 1ère administration: .....
Nombre total de dose(s) délivrée(s) : .....
Signes d'intolérance : ☐ oui ☐ non Préciser: .....

	Oui	Non	Délais (heures)	Durée (jours)
HBPM ou HNF				
Antibiotiques (Préciser)				
Corticoïdes				
SAT ☐ VAT ☐				

EXAMENS COMPLEMENTAIRES
Echo-doppler: ☐ oui ☐ non
Date et Heure: .....
Résultats: .....

SUIVI A J15	
Maladie sérique	Fièvre ☐ Eruption cutanée ☐ Polyarthralgies ☐ Adénopathies ☐ Autres☐
Signes biologiques à rechercher si signes cliniques présents	↑ VS ☐ Protéinurie ☐ Hématurie ☐ ↓ C3 ☐ ↓ C4 ☐ Immuncomplexes circulants à IgM et IgG ☐
Gêne fonctionnelle persistante	☐ oui Préciser : ..... ☐ non
Signes locaux (Préciser)	.....

PERMIS D'IMPRIMER

PERMIS D'IMPRIMER

THÈSE DE Madame JOLLIVET Virginie

Vu, le Directeur de thèse

BOELS David
PRATICIEN HOSPITALIER - PHARMACIEN
TOXICOLOGIE CLINIQUE
CENTRE ANTIPOISON - CHU ANGERS
daboels@chu-angers.fr

Vu, le Président du jury de thèse

F.G.

Vu, le Doyen de la
Faculté de Médecine
d'ANGERS

FACULTÉ DE MÉDECINE - ANGERS

Professeur I. RICHARD

Vu et permis d'imprimer