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Case report

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

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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.

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; Camou F et al., 2009; Chippaux JP, 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.,

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2009; Boels D et al., 2012): pain and local swelling in the event of minor envenomation; limb swelling, systemic symptoms and biological disorders in case of moderate envenomation; and extensive swelling spreading to the trunk and/or acute systemic symptoms in severe envenomation (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. 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® which 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), I (minimal envenomation), IIA and IIB (moderate envenomations) to III (severe envenomation). The grades were reassessed throughout the hospitalization period. The highest gradation 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, 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 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%):