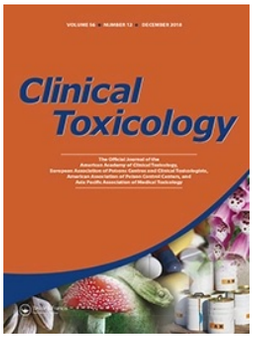

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REVIEW

Severe *Heloderma* spp. envenomation: a review of the literature

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ABSTRACT

Context: *Heloderma* bites are rare and generally mild, but a few cases can be life threatening. Methods: Description of *Heloderma* bite was searched in medical literature.

Discussion: We present a synthesis of clinical and biomedical effects of envenomation by *Heloderma* sp. based on 22 well identified cases described in medical literature. Three life-threatening syndromes, concomitant or not, may be involved: (a) angioedema which can lead to respiratory tract obstruction, (b) significant fluid losses due to diarrhea, vomiting and sweating, associated with hypokalemia and sometimes metabolic acidosis, and (c) atrioventricular conduction disorders simulating cardiac ischemia.

Conclusion: *Heloderma* bite are quite rare and generally mild. However, few severe cases may require emergency resuscitation. There is no antivenom, and the treatment is only symptomatic and supportive.

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Venomous lizard; envenomation; Heloderma suspectum; management

Introduction

Endemic to the southern United States, Mexico and northern Guatemala, the Helodermatidae family includes a single genus, *Heloderma* and five species *H. horridum* (Mexican beaded lizard), *H. suspectum* (Gila monster) and 3 species recently elevated from *H. horridum* subspecies: *H. alvarezii*, *H. charlesbogerti* and *H. exasperatum* [1,2]. It is the only group of lizards with specialized venomous glands situated in the lower jaw (Figure 1). The venom discharges through ducts ending close to grooved teeth that enable its inoculation. Devoid of muscle allowing expulsion of the venom, the latter penetrates into the bite by capillarity, greatly facilitated by the chewing action during the bite [3].

Heloderma do not use their venom to immobilize, kill and digest prey as most venomous animals do. Probably, the venom is primarily used as a defensive weapon [4], which is consistent with its remarkable genetic conservation despite an ancient separation of the *Heloderma* species (~30 Ma), as well as the composition and properties of the venoms from *Heloderma* species [5,6]. The venom contains about 50 distinct proteins, including kallikrein-like serine proteinases, phospholipase A_2, bioactive amines, and low molecular weight toxins [6–8].

Heloderma bite envenomation cases appear to be relatively rare although several authors believe that they could be underreported [9]. However, in addition to the trauma from the bite, envenomation can be severe and even life-threatening. A recent case of envenomation showing all the severe syndromes described after *Heloderma* bites [10], prompted us to look for similar cases in the literature. We compared the envenomations reported since the beginning of the twentieth Century to explain the pathogenesis of symptoms and to propose an appropriate management.

Methods

We searched PubMed and Google Scholar for medical and scientific publications using the words "*Heloderma*" and "*Heloderma* and bite", respectively, resulting in approximately 1200 references. We extracted 68 of them regarding *Heloderma* bite envenomation, venom composition, and pharmacology and experimental studies carried out with the venom. Then, we searched among the references cited in these publications, unreferenced documents that we obtained. Finally, we selected 43 articles for this study on the basis of their originality and relevant methodology or description.

Results and discussion

Most often, *H. suspectum* bites occur during capture or care of a captive specimen [7,11] while bites of *Heloderma horridum* sp. result either from an accident or from handling the animal. Bites are inflicted in the upper limb in more than 85% of the cases, in particular in the finger or hand (>80%). From a series of 105 *H. suspectum* bites in human, of which 79% were men, two-thirds of the victims were treated in health facility. Of these 71 patients seen in a health care facility, 17 (24%) were admitted. Eleven of these 17 admitted patients were in the ICU. Six had airway edema with two undergoing endotracheal intubation and one undergoing

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Figure 1. *Heloderma suspectum cinctum* Bogert & Martín Del Campo 1956 (Photo K. Amri).

cricothyrotomy after unsuccessful attempts at endotracheal intubation. These authors reported no death occurred in USA during a 12-year surveillance. Thirty deaths were mentioned until the 1940s [1,12], of which only 1 was confirmed and documented [13]. However, no deaths following *Heloderma* bite have been reported in the past 60 years.

We collected in the literature twenty-two documented Heloderma bites that are summarized in Table 1. Pain is constant and accompanied by regional ecchymotic edema of variable severity. Although the trauma of the bite can be significant, local lesions are usually moderate. Stahnke et al. [17] described hypoxic aspect of the bitten finger which they had attributed to a local arterial spasm; however, the patient had been treated before with local cryotherapy which may explain the spasm [18]. In another patient bitten in the hypothenar eminence, the radial pulse was impalpable while the Doppler showed normal arterial flow and venous return [18,19]. In most cases, general signs (diaphoresis, dizziness, nausea, vomiting) occur 5–15 min after the bite.

Biologically, the hemogram is little disturbed apart from neutrophilia [10,18,21,27]. Coagulation disorders are unusual and without clinically significant manifestations [20,23,24]. Hypokalemia can be clinically significant ($<3\ mmol{\cdot}L^{-1}$), generally asymptomatic, and associated with a moderate decrease in other blood electrolytes (phosphate, calcium, magnesium) [10,21,23,24]. Two cases reported transient metabolic acidosis of undetermined etiology [20,24].

Finally, 3 major syndromes are life threatening: (a) angioedema of the respiratory tract which can lead to their obstruction; (b) significant fluid losses through diarrhea, vomiting and diaphoresis, leading to electrolyte abnormalities, in particular hypokalemia and sometimes metabolic acidosis; and (c) atrioventricular conduction disorders simulating cardiac ischemia.

In humans, severe pain, in addition to the trauma of a prolonged bite, and hypotension result from the physiological effects of horridum toxin, helodermatin and gilatoxin which release bradykinin and angiotensins I and II [28,31–34]. Helodermatin also releases bradykinin, a potent vasodilator that causes a sudden drop in blood pressure, but does not degrade either fibrinogen or plasminogen [32]. The high and abrupt release of bradykinin could explain angioedema, the etiology of which remains unclear, especially since respiratory tract angioedema and vasoplegic shock are generally not associated with other allergic symptoms, especially skin symptoms (pruritus, urticaria, rash, etc.). This suggests non-allergic bradykinin angioedema rather than helodermatid venom anaphylaxis [35], as already suggested [10,29]. However, to our knowledge, immunoglobulins E were never assayed.

Cardiac conduction disturbances with signs of left ventricular ischemia are common in severe *Heloderma* envenomation. The analogy with *takotsubo* syndrome is relevant and the atrioventricular conduction disorders show similarities to *takotsubo* syndrome [10,18,19,22–24], in particular that described in severe scorpion sting envenomation in relation to the sympathetic and then parasympathetic effects due to scorpion venom [36,37]. Usually caused by acute stress, *takotsubo* syndrome appears to be related to an intense and sudden discharge of catecholamines, which is seen at the onset of the envenomation of the scorpion – and possibly *Heloderma* as well – which would cause temporary vasoconstriction of the coronary vessels. This hypothesis would explain the transient rise in blood pressure observed in some patients (personal communication, Scott Weinstein) [15], which is common in the onset of *takotsubo* syndrome.

Hematological abnormalities in blood clotting do not appear to have clinical translation [38]. Helodermatin, a potent proteinase, does not degrade either fibrinogen or plasminogen [39]. However, the decline in fibrinogen observed in few patients [10,23] can be explained by its degradation by gilatoxin [34] and the inhibition of platelet aggregation by phospholipase A_2 [39].

Several peptides belonging to the family of helospectins or helodermins, also called "mimetic incretin", are structural and pharmacological analogues of glucagon and vasoactive intestinal peptide (VIP). They induce a relaxation of smooth muscles and dilation of vessels, especially intestinal vessels, and increases the synthesis of cyclic adenosine monophosphate (cAMP) in enterocytes [8,40,41], enhancing the action of helodermatin and gilatoxin. Profuse diarrhea associated with hypokalemia observed in *Heloderma* bite envenomation suggests a pathological mechanism similar to pancreatic cholera (or Verner-Morrison syndrome) due to a tumor secreting VIP [8]. Helospectin is as effective but less powerful than VIP [8,42] unlike helodermin that is more powerful and has a longer duration of action than VIP [8,43].

An incretin analogue, exendin-4 (exenatide), a 39 amino acid peptide, rises pancreas β-cells proliferation and survival increasing insulin secretion, reduces glucagon secretion, slows down gastric emptying and decreases appetite, which contributes to an anti-diabetic effect [44]. Synthetic exenatide has been marketed since 2005 under the name Byetta® for the treatment of type 2 diabetes. It is noteworthy that reported side effects are similar to some symptoms of *Heloderma* envenomation such as nausea, diarrhea, vomiting, abdominal pain, dizziness, cardiac arrhythmia and angioedema. However, amazingly, hypoglycemia has never been reported after *Heloderma* envenomation.

The initial response in first aid is to detach the animal, that often is very difficult because of the tenacious grip commonly exerted when these lizards bite. The use of force,

Table 1. Comparison of documented helodermatid bite envenomations based on the literature.

References Symptoms	[3]	[10]	[13]	[14]	[15]		[16]	[17]	[18,19]	[20]	[21]	[22]
Species	H. s.	H. s. cinctum	H. s.	H. s.	H. s.	H. s.	H. h.	H. s.	H. s.	H. s.	H. s.	H. s.
Size (mm)	400	400	473	380	455	455	635	450				
Bite circumstances	Handling	Handling	Handling	Cage cleaning	Playing	Carriage in a bag	Handling	Handling	Handling	Carriage	Capture	Handling
Bite duration (seconds)		450	< 300	300	7		120	300	15			
Gender	Female	Male	Male	Male	Male	Male	Male	Male	Male	Female	Male	Male
Age (years)	50	39	50		29	32	39	27	20	29	40	25
Bite site	Finger	Forearm	Finger	Finger	Finger	Finger	Finger	Finger	Hand	Abdomen	Forearm	Hand
Pain	Yes	Yes	Yes	Intense	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Pain diffusion	Yes	Yes		Yes			Yes	Yes				
Dizziness	Yes	Yes	Yes					Yes		Yes		
Anxiety			Yes					Yes			Yes	
Diaphoresis	Yes	Yes	Yes							Yes	Yes	Yes
Diarrhea	Yes	Yes								Yes		
Limb edema		Yes	Yes	Yes	Yes						Yes	Yes
Dyspnea		Yes			Yes						Yes	
Agitation		Yes		Yes				Yes				
Angioedema		Yes								Yes	Yes	
Admission time (minutes)		40	90	30	30		30	40		20	60	10
Nausea		Yes				Yes	Yes	Yes				Yes
Vomiting		Yes					Yes			Yes		Yes
Cardiac frequency		118 ==> 180	88		92		120	90	70	150	80	0 ==> 110
Blood Pressure (mm Hg)		56/45- 106/65	142/80		190/90		137/86	90/60	135/70	52/* ==> 86/49	100/40	0 ==> 96/48
Heartbeat		Atrial fibrilation								Normal		Normal
Electrocardiogram		Ischemia							Anomalies		Normal	ST Anomalies
Oxymetry (%)		98										
White Blood Cells		26,000	8,100		11,700		Normal		14,000	8,200 / 24,800	25,000	5,700
Hemoglobin (g/dL)		15.2 / 16.9					Normal		16.4			14.8
Blood platelets		242,000 / 91,000					Normal		238,000	264,000/135,000	255,000	
Fibrinogen (g/L)		1.6 ==> 0.8							Normal		Normal	
PT*, PTT*		Low PT							Normal	Prolonged PTT	Normal	Normal
Fibrin Split Prod. (µg/mL)												
Proteinuria		Yes							Normal			Normal
Hematuria									Normal			Normal
Serum creatinine (mg/L)		Normal							Normal		Normal	Normal
CPK* (IU)		Normal							Normal			Normal
Hypokalemia		Yes								Yes	Yes	
Metabolic acidosis										Yes		
First improvement (hours)	1	24	20							17	8	
Overall regression (hours)	3	36	40				24			36	15	
Pain relief (hours)	1	48		12	24	2	2.5		Rapid			
Treatment		Adrenaline, electrical cardioversion, analgesics I/III, antibiotics	Antibiotics	Morphine, antibiotics	Adrenaline, morphine, analgesics II, antibiotics		Analgesics III, corticosteroids	Cryotherapy, analgesics II, antihistamine, edrophonium, antibiotics, local anesthesia	Antibiotics	Dopamine, antiemetic	Adrenaline, antihistamine, corticosteroids, O_2	Adrenaline, corticosteroids, antihistamine, analgesics III
Hospital time (days)	0	85	1.5	0.5			48	3	1	3	1	2
Recovery (days)	7	60	6		7	7		7			2	

References Symptoms	[23–24]		[25]			[26]	[27]	[28]	[29]	[30]
Species	H. s. cinctum	H. s.	H. s.	H. s.	H. s.	H. s.	H. h.	H. charlesbogerti	H. s.	H. s.
Size (mm)						500		470		300
Bite circumstances	Handling	Handling	Handling	Handling	Carriage in a bag	Handling	Handling	Handling	Handling	Handling
Bite duration (seconds)	90	900	20	7	< 5	2	30	15	600	10
Gender	Male	Male	Male	Male	Male	Male	Male	Male	Male	Male
Age (years)	23	20	51	29	23	37	40	24	29	41
Bite site	Forearm	Calf	Finger	Finger	Upper arm	Finger	Hand	Hand	Forearm	Finger
Pain	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Pain diffusion						Yes		Yes		
Dizziness	Yes	Yes			Yes	Yes	Yes	Yes		
Anxiety			Yes	Yes	Yes					
Diaphoresis	Yes		Yes		Yes	Yes	Yes	Yes	Yes	
Diarrhea										
Limb edema	Yes						Yes	Yes	Yes	
Dyspnea		Yes						Yes		
Agitation										
Angioedema							Yes	Tongue	Mild	
Admission time (minutes)	120	45	40		120	80		15		120
Nausea		Yes		Yes	Yes	Yes			Yes	
Vomiting	Yes	Yes		Yes			Yes	Yes	Yes	
Cardiac frequency	140	140	90	150		90	60	102		90
Blood Pressure (mm Hg)	76/54	108/60	90/60 - 156/96	60/* - 68/*		120/60	110/63	70/52		126/82
Heartbeat	Irregular PVCs							Irregular PVCs		
Electrocardiogram	Ischemia	Sinusal	Normal							
Oxymetry (%)							55	99		
White Blood Cells	48,300	21,500		11,400		Normal	18,500	12,600	13,900/ 27,300	Normal
Hemoglobin (g/dL)	18.6	19.4				Normal				Normal
Blood platelets	171,000 ==> 62,000	Normal				Normal				Normal
Fibrinogen (g/L)	0.68	Normal	3.8			Normal		Normal		Normal
PT*, PTT*	Elevated PT, PTT	Normal	Normal	Normal		Normal		Normal		Normal
Fibrin Split Prod. (µg/mL)	> 40		Normal			Normal				
Proteinuria										
Hematuria										
Serum creatinine (mg/L)	30					Normal				Normal
CPK* (IU)	4,697									Normal
Hypokalemia	Yes									
Metabolic acidosis	Yes									
First improvement (hours)	72	14	4	8				0.5		12
Overall regression (hours)	16	36			36	12	8	3		12
Pain relief (hours)	72	36				96	8	12		12
Treatment	Electrolytes, FFP, Adrenaline, lidocaine IV	Antihistamine, antibiotics	Analgesics I/II, antibiotics	Antihistamine, naloxone	Analgesics II, antibiotics	Morphine, antibiotics	Analgesics II/III, antihistamine, corticosteroids, antiemetic	Analgesics I, antihistamine, corticosteroids, antiemetic, antibiotics		antibiotics
Hospital time (days)	5	3	< 1	0.3		15	1	1		0.75
Recovery (days)			< 7	< 1	< 2			15		5

shaking the animal, spreading its jaws using a lever, driving a straw into its nostrils or sprinkling it with various liquids (alcohol, chloroform or petrol) are ineffective, time wasting, increase jaw pressure, and may injure the *Heloderma*, including breaking teeth in the wound [17,21,25]. It is possible to quickly pass a flame under the animal's neck or to immerse it in cold water, sometimes resulting in detachment within a few seconds [9,22,25,27]. In some cases, the *Heloderma* promptly and spontaneously detached, especially when placed on a firm supportive surface [11,15,18,25,26,30].

There is no antivenom against *Heloderma* venom. Russell [45] mentioned the existence of two experimental antivenoms manufactured by Arizona State University and the University of Southern California Medical Center for research purpose. However, they have never been further developed or marketed.

Treatment is purely symptomatic and supportive. The choice of analgesics will depend on the intensity of the pain. Analgesic doses of ketamine (intravenous bolus of 0.1–0.5 $mg \cdot kg^{-1}$ followed by an infusion of 1–2 $\mu g \cdot kg^{-1}$ per minute) may be helpful [46,47]. Wound care includes cleansing and a search for Heloderma teeth fragments [20,22,24,25,28,30]. Elevation of the bitten limb should relieve local edema. Shock may require fluid resuscitation with vasopressor amines (dopamine, adrenaline) if indicated, and electrolyte correction as needed. Cardiac conduction disorders caused by *Heloderma* envenoming normalize spontaneously with the treatment of shock and hypokalemia. More severe cases may require multiple treatments, as in the case we described (electrical cardioversion, low molecular weight heparin, β-blocker, inhibitor of converting enzyme and antiplatelet agent) [10].

Half of the patients (12 of 21) received a single (9 cases) or 2 antibiotics (3 cases). The indication was not specified but it seems that in most cases it was prophylactic. The significant trauma of the bite and the presence of numerous bacteria in the oral cavity of reptiles raise concerns about wound infection. However, there is a consensus to avoid the prophylactic administration of antibiotics in the event of a reptile bite because, (i) secondary infection is infrequent, (ii) prophylaxis seems ineffective, (iii) the benefit/risk ratio (in particular side effects and resistance) is unfavorable to antibiotics and (iv) it is preferable to choose them on the basis of the germ identification when local signs and the onset of fever suggest a secondary infection [48–50].

Conclusion

Heloderma sp. are quite rare, except in some areas, and mainly nocturnal or diurnal in spring and fall. They live in a restricted geographical area. This limits contact with humans and the risk of bites, apart from herpetologists or amateur collectors who handle them. Generally, the bite induces intense, radiating pain, associated with regional edema with variable severity, significant local wounds, and systemic disorders that are mild in most cases: dizziness, diaphoresis, nausea, vomiting, diarrhea.

However, envenomation can be severe, especially after a deep and prolonged bite that promotes the penetration of a large amount of venom. Angioedema, including vasoplegic shock, may be cause for concern and require prompt intervention. Hypovolemia can be severe, sometimes associated with hypokalemia and metabolic acidosis, requiring emergency resuscitation. Finally, cardiac disorders (arrhythmia and ventricular ischemia), appear to be transient, but can be life threatening.

In the absence of antivenom, treatment is only symptomatic and supportive, sometimes requiring intensive care for respiratory support, treatment of cardiac abnormalities and restoration of electrolyte disorders.

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Disclosure statement

No potential conflict of interest was reported by the author(s).

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