SNAKEBITE ENVENOMATION AND DEATH IN THE DEVELOPING WORLD

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The purpose of this review is to address the global incidence and management of snakebite envenomation and to describe the clinical characteristics and pathogenesis of envenomation by species of the family Viperidae, genera *Bothrops* and *Crotalus*, the most common venomous snakes in Brazil. We focus on the pathogenesis of the acute renal failure induced by these snakes. Envenomation after snakebite is an underestimated and neglected public health issue responsible for substantial illness and death as well as socioeconomic hardship to impoverished populations living in rural and tropical Africa, Asia, Oceania, and Latin America. In developed nations, snake bite typically occurs during recreational activities, whereas in developing countries it is an occupational disease more likely to affect young agricultural workers, predominantly men. Scarcity and delay of administration of antivenom, poor health services, and difficulties with transportation from rural areas to health centers are major factors that contribute to the high case-fatality ratio of snakebite envenomation. (*Ethn Dis*. 2009;19[Suppl 1]:S1-42–S1-46)

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INTRODUCTION

Envenoming from poisonous animals, particularly terrestrial venomous snakes, causes substantial illness and death and represents an economic hardship on poor, rural populations and healthcare systems of tropical and subtropical Africa, Asia, Oceania, and Latin America.[1–25] Although mortality from snakebite is estimated to be one-tenth that of malaria, no equivalent global snakebite control program exists. An international effort is necessary to focus global attention on this neglected and treatable condition.[17]

The World Health Organization (WHO) estimates that ≈2,500,000 venomous snakebites per year result in 125,000 deaths worldwide, 100,000 of which are in Asia and approximately 20,000 in Africa.[5,6] The true global incidence of envenomation and its severity remain largely misunderstood. Hospital-based data are likely to underestimate the incidence, the case-fatality ratio, and the overall contribution snakebites make to worldwide morbidity and mortality because most victims seek traditional treatment; these victims may die at home and their deaths remain unrecorded.[4,21]

The objectives of this review are to describe the worldwide incidence and treatment of snakebite envenomation, as well as clinical characteristics and the pathogenesis of common venomous snakebites in Brazil.

EPIDEMIOLOGY

Approximately 3000 species of snakes exist worldwide, and 410 are considered venomous.[18] The reported rate of bites from these snakes is high. In India alone, >200,000 cases of snakebite envenomation are reported each year, with an estimated 35,000–50,000 deaths.[15,24] In Pakistan, there are ≈20,000 snakebite deaths annually.[24] In Nepal, there are an estimated 20,000 snakebites and ≈200 deaths in hospitals annually, predominantly in the eastern Terai.[4,24] In Vietnam, from 1992 to 1998, there were an estimated 300,000 bites per year, and a case fatality ratio of 22% was reported among plantation workers bitten by Malayan pit vipers.[24] In Mynamar, there were 14,000 bites and 1,000 deaths in 1991.[24] Papua New Guinea has one of the world's highest incidence rates of snake bites.[17] In Africa, the annual incidence rate of snake bites in the Benue Valley of northeastern Nigeria is 497 per 100,000 population, with a case-fatality ratio of 12.2%.[4] In northern Africa, the species that causes most bites and deaths belongs to the family Viperidae, *Echis* sp (saw-scaled vipers), whereas in Asia most frequent envenomations result from bites by species of the Elapidae family, represented by the *Naja* sp (cobras) and *Bungarus* sp (kraits). In Central and South America, bites by *Bothrops asper* and *Bothrops atrox* (lance-headed pit vipers) predominate.[4] In Brazil, the most severe cases of snakebite result from envenomation inflicted by species of the family Viperidae, genera *Bothrops* and *Crotalus* (South American rattlesnake). From 1990 to 1993, the Brazilian Ministry of Health reported 65,911 snakebites.[1] Bites by snakes of genus *Bothrops* were responsible for 90.5%, and bites by *Crotalus* rattlesnakes accounted for 7.7% of these.

Bucaretchi et al[26] analyzed hospital records of 73 children aged <15 years who were bitten by *Bothrops* sp snakes in São Paulo, Brazil, from January 1984 through March 1999. Most bites occurred from October to March, which

reflects the influence of seasonal factors, such as an increase in temperature and humidity associated with the rainy season, and also in human agricultural activities, such as planting and harvesting. *Bothrops jararaca*, the most common species of *Bothrops* in southeast Brazil, which was responsible for most snake bites in this study, is more active during this season and in the evening. The rise in river levels due to tropical rains may cause an inland migration of these snakes.[3]

In developed countries, venomous snakebites frequently occur during recreational activities, whereas in the developing world, snakebite is an occupational disease more likely to affect young agricultural workers, predominantly men.[3,8,18,20] The high case-fatality ratio of snakebites in tropical developing countries is the result of a combination of factors, including the scarcity of antivenom, poor health services, and problems with transportation from rural areas to health centers.[4,17,19–23,27,28]

CLINICAL CHARACTERISTICS AND PATHOGENESIS

This section primarily focuses on the major clinical characteristics and the pathogenesis of envenomation by selected species of snakes that are highly prevalent in Brazil.

Bothrops sp (Lance-headed Pit Vipers)

Bothrops venom contains various biologically active peptides, such as metalloprotease, phospholipase, and hyaluronidases, which may elicit an inflammatory response and contribute to cell and tissue injury as well as hemostatic disturbances.[29–33] Most *Bothrops* venom activates coagulation factor X and prothrombin and lyses fibrinogen, which leads to hypofibrinogenemia and complete fibrinogen consumption. As a consequence, consumption coagulopathy and partial or complete blood incoagulability may develop. Envenoming by *Bothrops* sp inflicts severe tissue damage, such as swelling, blistering, hemorrhage, and necrosis of skeletal muscle. Systemic effects include spontaneous hemorrhage (of which cerebral hemorrhage is the most serious manifestation), disseminated intravascular coagulation, and cardiovascular shock secondary to hypovolemia and vasodilation,[1–3,7,16,26,29,34] *Bothrops jararaca* venom is a potent inhibitor of angiotensin-converting enzyme (ACE) and potentiates the hypotensive effect of circulating bradykinin. Murayama et al cloned and sequenced cDNA isolated from the *Bothrops jararaca* venom gland; it encodes 2 distinct classes of bioactive peptides, bradykinin-potentiating oligopeptides and a C-type natriuretic peptide, which display synergistic effects on blood pressure and most likely contribute to the cardiovascular effects caused by *Bothrops jararaca* envenomation.[35,36]

Crotalus (South American Rattlesnake)

Among the species of *Crotalus*, *Crotalus durissus terrificus* is the most frequently implicated in envenomation in Brazil. The venom of *C d terrificus* contains a variety of toxic peptides, including crotoxin, crotamine, giroxin, convulxin, and a thrombin-like enzyme. Crotoxin is responsible for the high toxicity of the venom and has neurotoxic, myotoxic, and nephrotoxic activity. It is a powerful presynaptic neurotoxin that targets neuromuscular junctions and inhibits the release of acetylcholine, which leads to neuromuscular blockade and progressive flaccid paralysis of variable degrees.[1,5,10–14] Crotoxin also produces severe skeletal muscle injury leading to rhabdomyolysis with the subsequent release of myoglobin from damaged skeletal muscle into serum and urine. High serum and urine levels of myoglobin are potentially nephrotoxic, leading to acute tubular necrosis, the primary and most serious complication of human crotalid envenomation.[5,10,13,37–39] Tissue damage at the site of the bite has been reported to be minimal or absent, a feature that differentiates the South American rattlesnake from other species of *Crotalus*. Spontaneous bleeding has only been rarely observed in human patients.[1,10,18]

A prospective survey of 100 cases of *C. durissus* bites followed from hospitalization to death or discharge in São Paulo, Brazil, revealed a high prevalence of acute renal failure (ARF) (29%), defined as a creatinine clearance <60 mL/min/1.73 m^2 in the first 72 hours after the bite.[5] Most cases of ARF were nonoliguric, and the fractional excretion of sodium was significantly higher in ARF patients. Age <12 years was an independent risk factor for ARF, which may be related to an increased concentration of the venom and a more severe clinical picture as a result of a lower blood volume and smaller body surface in children. The case fatality ratio was 10%. The most important finding in the study was that delay in administering an adequate dose of the crotalid antivenom increased the risk of ARF by more than 10 times. Therefore, Burdmann et al suggest that antivenom should be available in health centers and emergency services of small communities rather than concentrated in urban reference hospitals.

PATHOGENESIS OF SNAKEBITE-INDUCED ARF

Because it is well vascularized, the kidney is a particularly vulnerable organ to venom toxicity.[6] ARF is a serious complication of venomous snakebites by the Viperidae family.[1,5,10,24,25,40] Snakebite-induced ARF is usually caused by acute tubular necrosis, but all renal structures may be involved. Renal cortical necrosis, acute tubuloin-

terstitial nephritis, extracapillary proliferative glomerulonephritis, mesangiolysis, and vasculitis have all been described.[6,9,34,40–43] A myriad of nephrotoxic insults have been implicated in the pathogenesis of ARF, such as nephrotoxicity of venom, hypotension, circulatory collapse, precipitation of endogenous pigments such as myoglobin and hemoglobin in renal tubules, disseminated intravascular coagulation, sepsis, hemodynamic alterations, and cell injury induced by the release of proinflammatory cytokines and vasoactive mediators.[6,9]

Experimental models have been attempted to clarify the renal involvement in snakebites. In the perfused rat isolated kidney model, Castro et al[44] showed that *Bothrops jararaca* venom directly injures proximal tubules, evidenced by a decrease in glomerular filtration rate and renal plasma flow and an increase in renal vascular resistance and fractional excretion of sodium.

Further experimental studies[45] have shown that the intraperitoneal injection of *Bothrops jararaca* venom in rats induced recruitment of polymorphonuclear leukocytes (PMN) into the peritoneal cavity and that pretreatment with anti-mouse intercellular adhesion molecule-1 (ICAM-1), platelet endothelial cell adhesion molecule-1 (PECAM-1), and leukocyte endothelial cell adhesion molecule-1 (LECAM-1) significantly reduced the number of recovered PMN. *Bothrops jararaca* venom induced a marked increase in peritoneal leukotriene B4, thromboxane A2, interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α). These results suggest that the PMN influx induced by intraperitoneal injection of *Bothrops jararaca* venom in mice is related to the expression of ICAM-1, PECAM-1, and LECAM-1 adhesion molecules, which are responsible for the rolling, firm adhesion, and transmigration of PMN and that these effects may be indirect through the release of leukotriene B4, thromboxane A2, TNF-α, and IL-6. The study also points out to the potential ability of *Bothrops jararaca* venom to activate the endothelium, since adhesion molecules are expressed by endothelial cells.

Snake venom metalloproteinases, abundant enzymes in crotaline and viperine snake venoms, administered to experimental animals trigger a cascade of inflammatory events, such as release of interleukin-1 (IL-1) and IL-6, activation of the classic and alternative complement system pathways, and increased expression of mRNA encoding for TNF-α, IL-1, and IL-6 by elicited macrophages.[30,31,33]

In the perfused rat isolated kidney model, Martins et al[46] demonstrated that inhibition of synthesis of cytotoxic mediators, possibly TNF-α, by thalidomide and pentoxyfilline reversed all renal alterations induced by supernatants of macrophages activated with *C durissus cascavella* venom. Martins et al were also able to demonstrate that the cyclooxygenase inhibitor indomethacin reversed almost all renal alterations induced by supernatants of macrophages stimulated by *C d cascavella* venom. The fact that the supernatant of macrophages is free of venom, as shown by high performance liquid chromatography analysis, strongly suggests that the venom itself is not acting directly but rather that the macrophages are releasing mediators, which can promote nephrotoxicity.

TREATMENT

Antivenom is the only specific antidote to snake venom and its timely administration completely reverses all systemic manifestations of envenoming.[1,4–6,23,25,47] Adverse reactions are frequent (as high as 87%), may include anaphylactic shock, and cannot be predicted by sensitivity tests.[47,48]

Besides antivenom administration, the treatment of snakebite envenoming includes a number of additional interventions, such as maintenance of fluid, electrolyte balance, and good urine flow; administration of tetanus toxoid; assisted ventilation; dialysis; use of acetylcholinesterase inhibitors, preceded by atropine sulfate, in neurotoxic envenomations; early alkalinization of urine by sodium bicarbonate in patients with myoglobinuria or hemoglobinuria; antibiotics in case of development of local infection; and surgical débridement of necrotic tissue. Atropine sulfate counteracts the muscarinic effects of acetylcholine, such as increased respiratory secretions, sweating, bradycardia, and colic.

The use of tourniquets should be discouraged. In envenomations from *Bothrops* sp, the venom of which possesses cytolytic and necrotizing activity, tourniquets increase the retention of the venom at the bite site and may enhance the extent of local injury.[1,7,24,49] Pressure immobilization is recommended for bites by neurotoxic elapid snakes but should not be used for viper bites.[24] Fasciotomy is only indicated to treat intracompartmental syndrome after the hemostatic abnormalities are properly corrected.[1,4–6,9,18,24,25]

New approaches have been developed to improve the quality of antivenom, such as using DNA immunization or the purified relevant toxins as antigens instead of the whole venom; searching for other animal species from which it is possible to obtain antivenom, such as camels and hens; preparing antivenom that combines antibodies with recombinant ''nanobodies,'' which, by having a very low molecular mass, may reach tissue compartments more rapidly than conventional immunoglobulin G fragments.[4,27]

Although antivenom is extremely efficient in the neutralization of systemic abnormalities, the amelioration of venom-induced local effects is difficult because of the rapid development of tissue injury after envenomation and the delay in reaching health centers where

antivenom is available. As a result, permanent sequelae develop in a number of snakebite patients.[4]

An experimental study has recently shown that the administration of either the peptidomimetic matrix metalloproteinase inhibitor batimastat or the chelating agent EDTA to the subplantar hindpaw region of rats rapidly after venom injection abrogates hemorrhagic and dermonecrotic activities of *Bothrops asper* venom.[29] Rucavado et al suggest that the administration of these drugs at the site of venom inoculation may represent a useful alternative in the neutralization of venom-induced local tissue injury.

CONCLUSION

Snakebite is an underestimated and ignored public health problem that causes considerable illness, death, and socioeconomic hardship to poor populations living in rural tropical regions of the globe where access to life-saving antivenom is poor. There is an urgent need to acquire knowledge of the epidemiology of snakebite envenomation around the world and to promote public health policies directed to improving the treatment and prevention of envenomation.

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