Special Communication

Snake Venom Poisoning in the United States

Experiences With 550 Cases

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SNAKE venom poisoning is a medical emergency requiring immediate attention and the exercise of considerable judgment. Approximately 45,000 snakebites occur each year in the United States, of which almost 8,000 are inflicted by venomous snakes, and about 6,800 of these are reported.[1,2] During the past five years, the number of deaths from snake venom poisoning in this country has not exceeded 12 each year. Approximately 20% of all bites by venomous snakes in the United States show no evidence of envenomation; that is, the offending reptile bites but does not inject venom or ejects it onto the skin during a superficial strike. This percentage is even higher with elapids (cobras and corals, among others), and there is no doubt that many of the "cures" described in the literature[3] can be ascribed to the fact that no envenomation took place during the biting. Thus, it is important that the admitting physician note whether the bite has been inflicted by a venomous or nonvenomous snake, and if the former, whether or not envenomation has occurred. The identity of the offending reptile, when obtainable, should be noted on the hospital record.

While there are more than 3,000 species of snakes, only 300 or so can be considered sufficiently poisonous to be of danger to man. In the United States, there are approximately 120 species of snakes, about 20 of which are venomous. The venomous species include the rattlesnakes (*Crotalus*), cottonmouths or water moccasins, and copperheads (*Agkistrodon*), pigmy rattlesnakes and massasaugas (*Sistrurus*), all members of the family Crotalidae, and the eastern coral snake (*Micrurus*), and the small and relatively unoffensive Arizona coral snake (*Micruroides*), both members of the family Elapidae. Whenever possible, positive identification of the snake should be made by a trained person. The proper identification of a venomous species is not always easy, and when the offending snake is not captured, or even seen, the physician will need to give very careful attention to the development of the symptoms and signs.

There are some distinguishing features of note for identifying poisonous snakes. The crotalids and viperids are distinguished from the nonvenomous snakes by their two elongated, canaliculate, upper maxillary teeth, which can be folded against the roof of the mouth. The fangs of the coral snakes are also elongated, upper anterior maxillary teeth, but they are proportionately much shorter and fixed in an erect position. In the crotalids, the pupils are vertically elliptical, but a few nonvenomous snakes also have such pupils. Most dangerous elapids have round pupils. The crotalids have a deep, easily identifiable pit between the eye and the nostril, which is a heat-receptor organ. The somewhat triangular shape of the head of most of the crotalids may also help to distinguish them from nonvenomous snakes. Color and pattern are the most deceptive criteria for identification. Unfortunately, these are the characteristics most uninformed persons will present.[4-6]

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CHEMICAL PROPERTIES

It is not the purpose of this article to discuss the chemical, physiopharmacological, and immunological properties of snake venoms. The reader is referred elsewhere for a thorough review of these problems.[7-10] Certain general principles, however, should be noted. The venoms of snakes are complex mixtures, chiefly proteins, many of which have enzymatic activities. During recent years, it has been shown that the lethal and perhaps more deleterious fractions of snake venoms are certain peptides and proteins of relatively low molecular weight. They range in molecular weight from less than 6,000 to approximately 30,000; some of them are 5 to 20 times more lethal than the crude venom. The peptides appear to have very specific receptor sites, both chemically and physiologically.

The role of these peptides in snake venom poisoning has been too often overlooked by physicians, who have mistakenly assumed that snake venoms are only "enzymes" and thus have employed therapeutic measures that have not only been inconsistent with our knowledge of the chemistry and pharmacology of these complex poisons but that have also led to unfortunate clinical errors. The once proposed measure known as cryotherapy failed to account for the presence of these peptides and also entertained the equally erroneous opinion that the activity of all enzymes can be reduced by cooling. Also, if one wished to reach the temperatures in tissues necessary to reduce the activity of a few of the snake venom enzymes on which we have data, deleterious tissue changes would be noted, as attested to by the number of amputations and the tissue destruction brought on by this measure.

However, snake venoms are rich in enzymes. Some of the more important are proteinases; L-arginine-ester hydrolases; transaminase; hyaluroni-

dase; L-amino acid oxidase; cholinesterase; phospholipase A, B, C, and D; ribonuclease; deoxyribonuclease; phosphomonoesterase; phosphodiesterase; 5′-nucleotidase; adenosine triphosphatase; alkaline phosphatase; acid phosphatase; nicotinamide-adenine dinucleotidase; and endonucleases.

PHARMACOLOGIC PROPERTIES

The common practice of dividing snake venoms into such groups as neurotoxins, hemotoxins, and cardiotoxins, perhaps serving some purpose in classification, has led to much misunderstanding and to errors in clinical judgment. Chemical, pharmacological and clinical studies have shown these divisions to be both superficial and misleading. The so-called neurotoxic venoms may produce considerable cardiac or vascular changes, or have a direct effect on the blood. The so-called hemolytic venoms may also produce changes in the nervous system or in vascular dynamics.[7] As Reid[11] put it: "The dogma that cobra bites are neurotoxic—based on laboratory experiments in small animals—is still widespread. In fact, neurotoxic effects in human victims are rare; the main clinical feature of poisoning is local necrosis."

While this may be questioned in some cobra venom poisoning cases, Reid's point is well taken: snake venoms are complex mixtures, and the physician attending a patient with snake venom poisoning must remember that he is faced with a case of multiple poisoning, perhaps three or more toxic reactions, with changes that may occur simultaneously or sequentially. It should also be remembered that the effects of various combinations of the venom components, and of the metabolites formed by their interactions, can be complicated by the response of the victim. The release of autopharmacological substances by the envenomated patient may complicate the poisoning and make treatment more difficult.

The venoms of the rattlesnakes, and of many of the vipers, produce deleterious local tissue changes, changes in the blood cells, defects in coagulation, injury to the intimal linings of vessels, and, to a lesser extent, changes in resistances in the blood vessels. Pulmonary edema is common in severe poisoning, and bleeding phenomena may occur in the lungs, peritoneum, kidneys, heart, and elsewhere. These changes are often accompanied by alterations in cardiac dynamics and renal function. Factors responsible for renal failure include decreased glomerular filtration, hemolysis, hemoglobinuria, and the direct effect of the venom on the kidneys. Most of the crotalid venoms produce relatively minor changes in neuromuscular transmission, the notable exception being the venom of the Mojave rattlesnake, which also produces far less tissue destruction than most other rattlesnake venoms.

The early cardiovascular collapse seen in an occasional patient bitten by a rattlesnake is due to a marked decrease in circulating blood volume and perfusion failure. Although cardiac dynamics may be disturbed, in most cases the heart changes are secondary to the changes in circulating blood volume. Coral snake venom causes more extensive changes in the nervous system, but death may occur from cardiovascular collapse quite apart from the neurotropic changes.

CLINICAL FINDINGS

The symptoms, signs, and gravity of envenomation are dependent on a number of factors: (1) the nature, location, depth, and number of bites; (2) the amount of venom injected; (3) the species and size of the snake involved; (4) the age and size of the victim; (5) the victim's sensitivity to the venom; (6) the microbes present in the snake's mouth; and (7) the kind of first aid treatment and subsequent medical care. Snake bites may therefore vary in severity from trivial to extremely grave. Again, it should be emphasized that the patient can be bitten by a venomous snake yet not be envenomated.

Following poisoning by most of the Crotalidae, there is almost immediate swelling. Edema is usually seen around the injured area within five minutes after the bite. It progresses rapidly and may involve the entire injured extremity within an hour. Generally, however, edema spreads more slowly, usually over a period of 8 to 36 hours. The swelling is most severe after bites by the eastern diamondback rattlesnake, less severe after western diamondback bites and those by the prairie, timber, red, Pacific, Mojave, and black-tailed rattlesnakes, and sidewinders. It is least severe after bites by copperheads, massasaugas, and pigmy rattlesnakes.

Ecchymosis and discoloration of the skin often appear in the area of the bite within several hours. Vesiculations may be found within three hours. Generally, they are present at 24 hours. Hemorrhagic vesiculations and petechiae are common. Thrombosis may occur in superficial vessels, and sloughing of injured tissues is not uncommon. Necrosis develops in many untreated victims. Amputation of an extremity or part of an extremity is less common today than it was even a decade ago, largely because of the decrease in lapse of time between bite and medical treatment.

Pain immediately following the bite is a complaint of most patients with poisoning by North American rattlesnakes. It is most severe after eastern and western diamondback bites, less severe after bites by the prairie and other *viridis* rattlesnakes, and least severe after Mojave rattlesnake, copperhead, and massasauga bites. Weakness, sweating, faintness, and nausea are common. Regional lymph nodes may be enlarged, painful, and tender. A common complaint following bites by the Southern Pacific rattlesnake, and one sometimes reported after other pit-viper bites, is tingling or numbness over the tongue and mouth or scalp, fingers and toes, and around the wound. Hematemesis, melena, changes in salivation, and muscle fasciculations may be seen. Hematological findings may show hemoconcentration early, then a decrease in red blood cells and platelets. Urinalysis may disclose hematuria, glycosuria, and proteinuria. Bleeding and clotting times are usually prolonged.

TREATMENT

To be effective, treatment must be instituted immediately. However, it is not a purpose of this article to detail the various immediate and first aid measures for snake venom poisoning. We have done this elsewhere.[12-16]

The method of grading rattlesnake

bites by numbers on the basis of certain symptoms and signs has proved inadequate. Every finding should be considered significant in determining the severity of the poisoning. Pain, swelling, ecchymosis, and local tissue changes may be absent or minimal, even after a lethal injection of some rattlesnake venoms, and these findings are too commonly employed as the sole guides for grading envenomation. For that reason, we prefer to grade the poisoning as minimal, moderate, or severe, bearing in mind all clinical manifestations, including changes in the blood cells and chemistry, changes in motor and sensory function, and the like. In a study of 25 fatal cases of rattlesnake venom poisoning graded on the basis of one of the several number systems, nine had been diagnosed on admission, or during the first eight hours of hospitalization, as being only "grade 1" or "grade 2" poisonings. The grading had been done on the basis of pain, swelling, ecchymosis, and local tissue changes.

First Aid

In no case should any first aid measure be regarded as a substitute for antivenin or medical care, nor should it be instituted at the possible expense of delaying administration of antivenin. In bites by crotalids, if the patient arrives at the hospital 30 minutes or more after the bite, he should be put to bed, the wound cleaned thoroughly, and the injured part immobilized in a position of function. After such a time delay, incision, suction, excision, and other such measures are of little value. The extremity should not be packed in ice.

If the patient is seen within 30 minutes of a rattlesnake or cottonmouth bite, a constriction band, occluding superficial venous and lymphatic return but not arterial or deep venous flow, should be placed proximal to the bite or above the first joint proximal. It can be moved in advance of the swelling. The constriction band should be used in conjunction with incision and suction in viper bites, and removed as soon as antivenin administration has been started. Incision through the fang marks and suction are of value when applied immediately following bites by the pit vipers of North America. They are of lesser value following bites by the South American and Asiatic vipers, and probably of little value subsequent to envenomation by the elapids and sea snakes.

In rattlesnake bites, longitudinal incisions 3 to 6 mm in length should be made through the fang marks. The incisions should be made as deep as the fang penetration, which in most cases is very superficial. Suction should then be applied and continued for the first hour following the bite. Multiple incisions over the involved extremity or in advance of progressive edema are not advised. To be effective, suction must be started within a few minutes of the bite.

Although the tourniquet is said to be of questionable value in poisoning by elapids, in severe envenomation a tight tourniquet might be applied proximal to the bite and left in place until antivenin has been started. It should be released for 90 seconds every ten minutes. When the tourniquet is released, the physician should be prepared to treat immediate circulatory collapse. The injured part should be kept below the level of the heart but not in a completely dependent position. The patient should be kept warm. He should not be allowed to walk or be given alcohol, and reassurance should be given.

Medical Treatment

On admission to the hospital the necessary laboratory tests should be done. The choice of tests depends on the type of venom poisoning. In general, the following procedures should be carried out immediately: typing and cross-matching; bleeding, clotting, and clot retraction times; complete blood cell count; hematocrit determination; platelet count; and urinalysis. We frequently obtain red blood cell (RBC) indexes, sedimentation rate, prothrombin time, arterial blood gas measurements, and determinations of sodium, potassium, and chloride. In severe poisonings, it is advisable to get an electrocardiogram. Serum protein levels, fibrinogen titer, partial thromboplastin time, and renal function tests are often useful. In severe envenomation by rattlesnakes, the hematocrit value, blood cell count, hemoglobin concentration, and platelet count should be obtained several times a day for the first few days, and all urine samples should be examined, particularly for RBCs.

During the first 24 hours, as a guide to antivenin administration, measurement of the circumference of the injured part just proximal to the bite and some point above that should be recorded every 15 to 30 minutes. Measures for combating shock should be readily available. In severe envenomations, equipment for endotracheal intubation or tracheostomy and a positive-pressure breathing apparatus should be in readiness.

Administration of Antivenin.—The importance of early administration of antivenin, preferably intravenously, for many types of venom poisoning cannot be overemphasized. The choice of antivenin and the amount to be given will depend on the species and size of snake involved, the site of envenomation, the size of the patient, and a number of other factors. In rattlesnake bites, polyvalent crotaline antivenin (Antivenin [Crotalidae] Polyvalent) is the antitoxin of choice. The effectiveness of intravenously administered antivenin was first demonstrated in separate series of cases by one of us (F.E.R.) and by Gennaro and McCullough at a meeting of the Ad Hoc Committee on Snakebite Therapy of the National Academy of Sciences in December of 1960. The recommendations have subsequently been advocated by most other workers.

An antivenin for North American coral snake venom is also available, and there are more than 30 producers of other snake antivenins. In the United States, when the offending snake is an imported species, the physician should consult the nearest Poison Control Center for guidance on the availability and choice of antivenin. The larger zoos of the country usually stock supplies of antivenins and have emergency programs for dispensing them and addresses of consulting physicians. A national Antivenin Index is maintained by the Oklahoma City Zoo (405-424-3344), and the Los Angeles County/University of Southern California Medical Center maintains a consultation service for physicians. This Center is no longer able to provide antivenin

for patients sensitive to horse serum.

In minimal rattlesnake venom poisoning, and following the appropriate skin or eye tests for sensitivity, 1 to 4 units (vials or packages) of antivenin will usually suffice. In moderate cases, 4 to 7 units may be required, whereas in severe cases, up to 15 or even more units may be needed. Poisoning by water moccasins usually requires lesser doses, whereas in copperhead bites, antivenin is rarely required, except for children and the elderly. Antivenin can be diluted in saline or glucose solutions. In cases of shock, the antivenin should always be given intravenously. Under no circumstances should antivenin be injected into a finger or toe. It is not known how long after envenomation antivenin can still be effective. Recent studies indicate efficacy when given within four hours of a bite; it is of less value if delayed for eight hours, and of questionable value after 24 hours, except perhaps in poisoning by certain elapids. However, it seems advisable to recommend its use up to 24 hours in all severe cases of snake venom poisoning.[17]

Other Measures.—A decrease in circulating blood volume and perfusion failure is a common finding in all severe and most moderate cases of snake venom poisoning, particularly after rattlesnake envenomation. There may also be a concomitant lysis of RBCs and loss of platelets, necessitating transfusions and parenteral fluids. In cases with hypovolemia, plasma or albumin may be used to restore circulatory blood volume. If there is evidence of a decrease in RBC mass, either from lysis of RBCs or bleeding, packed blood cells or whole blood should be given. Where these complications are accompanied by defects in hemostasis, including coagulopathies, then replacement with specific clotting factors, fresh whole plasma, or platelet transfusions may be indicated.

A broad-spectrum antimicrobial agent should be given if there is severe tissue involvement. The appropriate antitetanus agent should be given. Aspirin, codeine, or meperidine hydrochloride may be given for pain. At the first signs of respiratory distress, oxygen should be given and preparations made for assisted or controlled ventilation. Tracheal intubation or tracheostomy may be indicated. The routine measures for the treatment of acute renal failure should be followed if this develops. Renal dialysis may be necessary. Peritoneal dialysis has been of little value in our experience; however, it is said to have been used successfully in severe cobra venom poisoning. Mild sedation may be indicated in all severe bites and when respiratory depression is not a problem. In shock, fluid replacement is indicated and inotropic agents may be required. The effectiveness of corticosteroids in venom shock states is unresolved. It is our clinical impression that steroids have little, if any, effect on the local tissue response to rattlesnake venom. They are the drugs of choice for treating subsequent reactions to antivenin. Antihistamines are of no proved value during the acute stages of poisoning, except when it might be decided to give one intravenously before administering antivenin in a sensitive patient. Isolation-perfusion of an extremity and intra-arterial infusion with antivenin have been tried with indifferent results.

Management of Wound.—The wound should be cleansed and covered with a sterile dressing. The injured part should be immobilized in a physiologic position. Ice bags, isolated from the skin by towels, afford some local pain relief, but they should not be applied while antivenin is being given or for the first few hours thereafter. Under no circumstances should an extremity be placed or packed in ice. Surgical débridement of blebs, bloody vesicles, and superficial necrosis may have to be performed between the third and tenth days. Most of these changes appear between the second and fifth days, and have usually reached maximal development by the fifth to ninth days. Débridement may need to be done in stages. Once it has been initiated, the patient should be examined for joint motion, muscle strength, sensation, and girth measurements. Immobilization should be interrupted by frequent periods of gentle exercise, progressing from passive to active.

Follow-up Care.—Follow-up care should include sterile whirlpool treatment, débridement as necessary, daily cleansing of the wound followed by several 15-minute soaks in 1:20 Burow solution, and daily painting of the wounds with an aqueous dye containing brilliant green 1:400, gentian violet 1:400, and acriflavine 1:1,000. An antimicrobial ointment can be applied at bedtime. Daily exposure of open lesions to continuous oxygen flow in a plastic bag is of value. Recent clinical experiences with hyperbaric oxygen indicate its value in some cases. Fasciotomy should be discouraged. We have not observed the need for this measure in the early management of more than 500 cases of snake venom poisoning. This measure usually reflects the use of an insufficient dosage of antivenin during the first 12 hours of the poisoning. It may need to be done when early antivenin treatment has been inadequate and there is substantial evidence of vascular impairment.

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