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REVIEW ARTICLE

Cobra Venom: A Review of the Old Alternative to Opiate Analgesics

Paul F. Reid, PhD

Pain has been called the fifth vital sign, and chronic pain impacts the lives of millions. The search for better analgesics is at a fever pitch, but opiates still dominate the moderate to severe pain treatment spectrum, and morphine, essentially a 2000-year-old drug, is still the gold standard. By today's pharmaceutical standards, opiates are old hat, and physicians are generally reluctant to prescribe them due to their potential for adverse effects and abuse. It is suggested that a new look at another old solution, cobra venom, could inject new life into pain management. This review looks at the historical use of cobra venom to control moderate to severe pain and at recent understandings of its mechanism of action. (*Altern Ther Health Med.* 2011;17(1):58-71.)

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Disclosure
Paul F. Reid, PhD, is a stakeholder in ReceptoPharm, which develops therapeutic products from cobra venom.

Cobra venom has been employed historically to relieve moderate to severe pain. Pain has been reported as the single most common reason patients seek medical care. Chronic pain affects more than 50 million Americans. In the United States, 42% of the population has experienced chronic pain lasting more than 12 months. The World Health Organization (WHO) has developed a three-step ladder to treat pain based on mild, moderate, or severe pain. Under the WHO 2008 Principals of Pain management, pain is measured on a scale of 1 to 10 with 1-3 being mild pain, 4-7 being moderate pain (interferes with work or sleep), and 8-10 (interferes with all activities) representing severe pain.[1] The National Sleep Foundation reports that more than 42 million people lose 2 or more nights of sleep due to pain, which, by definition, means they have moderate pain.

Chronic low back pain is the biggest problem and affects 27% of those with chronic pain, followed by headache (15%) and neck pain (15%).[2] It is the treatment of neuropathic pain that represents the gold standard for new analgesics, having its biggest impact on diabetics and patients with other neuralgias.[3] Rheumatoid arthritis, a disease that affects 1% of the world's population, also represents a large target for analgesics, especially analgesics with antiinflammatory activity.[4] The majority of emerging therapies for the treatment of moderate to severe pain are reformulations of existing pain medications combined with new delivery technologies that may offer only incremental improvements in efficacy and safety.

The estimated cost of pain to the US economy is over $100 billion, with more than $20 billion being directly spent on analgesics.[5] The report provides estimates that 51 metric tons of oxycodone and 39 metric tons of morphine were consumed worldwide in 2007.[6] Of all countries, the United States had the highest total consumption of oxycodone in 2007, followed by the United Kingdom, Canada, Denmark, Australia, and Norway. However, the abuse of prescription opiates has risen dramatically in the United States.[7,8] Interestingly, opiate use in developing nations is very low, possibly a consequence of cost and accessibility. At this time, the greatest need in the treatment of chronic pain is for agents that surmount the disadvantages of nonsteroidal antiinflammatory drugs (NSAIDs) and opioid analgesics.

In this review, it is proposed that a reexamination of the historic use of cobra venom in pain control may offer a future alternative for chronic pain management. Probably the first recorded use of cobra venom documented the suicide of Cleopatra. Cobra venom has allegedly been used for centuries in traditional Chinese and Indian medicine, with an early reference to use of serpents in English medicine in 1702 and the use of cobra venom in Hindu medicine for treating drug addiction.[9] The use of cobra venom in medicine goes back to the 1830s, when cobra venom was introduced into Western medicine as a homeopathic product. In homeopathic practice, high dilutions of potential poisons are used to induce a therapeutic response on the basis that like could treat like (*similia similibus curantur*). Unusually high dilutions (10^{-60}) of the drug are used such that it is unlikely that even a single molecule of the original substance remains in the final preparation. Consequently, homeopathy has suffered from an absence of credibility within the community of allopathic physicians.

Cobra venom was unusual in that it was clinically tested ("proved") at 0 (raw venom, no dilution) to the 10^{-12} dilution where its application evolved into a use primarily for pain.[10] Such

were its indications in Clarke's *Materia Medica* of 1900, the text that has become the principal reference text for the US and European Homeopathic Pharmacopeias.[11] Early in the 1900s, various viper venoms were being assessed in the clinic for the treatment of pain and epilepsy.[12,13] It was about that time that several researchers established that cobra venom had cytotoxic properties which quickly lead to studies in patients with cancer where its relief of pain was the dominant pharmacodynamic activity.[14] In the United States, the concept of using cobra venom as an analgesic was adopted by Macht,[9] who initiated several preclinical and clinical investigations but more importantly began to standardize the potency of the venom preparation.

SOURCES OF COBRA VENOM

Hooded cobras (Family *Elapidae*, Genus *Naja*) are old world snakes that range from Africa to Southeast Asia. Early in the last century, cobras were divided into three main groups: African cobras (with several species), the Asian cobra (*N tripudians*), and the King cobra (*Ophiophagus Hannah*). Due to the highly variable nomenclature of Asian cobras, the species known as *N tripudians* and later *N naja* has been replaced by more accurate classification into 10 species based on DNA analysis (Table 1).[15] An additional complication when studying the literature on the scientific use of such venoms stems from the geographical variation that occurs within the venom composition of the same species[16] that could render antivenoms useless.[17] From a medical standpoint the most important species are *N naja, N kaouthia,* and *N atra.*

TABLE 1 Reclassification of *Naja tripudians/Naja naja*

Original Name	Diversified Into	Common Name
Naja tripudians, then *Naja naja*	*Naja naja*	Indian cobra
	Naja kaouthia	Thailand cobra
	Naja atra	Chinese cobra
	Naja siamensis	Thailand spitting cobra
	Naja oxiana	Central Asian cobra
	Naja phillipinensis	Philippine cobra
	Naja samarensis	Southeastern Philippine cobra
	Naja sputatrix	Javan spitting cobra
	Naja sumatrana	Sumatran cobra
	Naja mandalayensis	Burmese cobra

Cobras produce about 0.3 mL of viscous venom per "milking" that is a complex mixture of proteins to subdue and kill prey. The venom is rapidly freeze-dried, thus preserving the vast majority of its biological activity. In this state, cobra venom is very stable, retaining its toxicity for decades. While the venom contains many different proteins, it has a particularly high content of small basic peptides ranging in size from 4 to 14 kDa that comprise about 70% of the protein content. Within this basic fraction can be found the neurotoxins that give cobra venom its neurotoxic trait. Cobra venom does not cause the prolific hemorrhage and tissue damage associated with most viper and rattlesnake envenomations.

Of particular interest in this review are the neurotoxins found in these venoms, although some neurotoxins are far more toxic than others. There are neurotoxins that affect the nicotinic cholinergic systems, the principal ones being cobratoxin (CATX, 7.8 kDa, 71 amino acids) and cobrotoxin (COTX, 6.7 kDa, 60 amino acids) that are nonenzymatic.[18] They function to block the attachment of acetylcholine and activation of the nicotinic receptor and represent about 10% to 15% of the venom composition. CATX the major neurotoxin in *N naja* and *N kaouthia* venom, though this neurotoxin may be absent from this species due to geographical variation (unpublished data). COTX is also found in the venom of *N naja* and *N kaouthia*, representing the primary neurotoxin in other cobra species. There are also neurotoxic phospholipases such as Nigexine (14 kDa, 119 amino acids) that block the activity of acetylcholine but also directly disrupt the cell membrane.[19] Other less toxic peptides (8 kDa) target the muscarinic acetylcholine receptors. Toxins that block calcium and voltage-activated potassium channels have also been described in cobra venom that mimic the activity of dendrotoxins from mambas and beta-bungarotoxin from kraits.[20,21]

PRECLINICAL STUDIES

Pharmacodynamics

With the introduction of any new analgesic, attention is often focused on the mechanism of action. In writing this review, that challenge became manifest. While our understanding of pain pathways has improved greatly, the mechanism of action of many analgesics is still the research foundation for many laboratories. Prior to any attempt to propose a plausible mechanism of action for the analgesic activity of cobra venom, it will be necessary to make several assumptions based on the available data. Firstly, the basis of the venom's activity is associated primarily with the principal neurotoxins that comprise approximately 20% to 25% of the venom. Secondly, the primary receptor targets for these neurotoxins are nicotinic acetylcholine receptors (NAchRs) although there may be some unrelated receptor involvement and other venom peptides will affect receptors distinct from NAchRs. NAchRs are sodium channels that are activated by acetylcholine and drugs like nicotine (agonists) that serve to translate a chemical signal into an electrical one. They are blocked (antagonized) by neurotoxins such as those from cobras because such neurotoxins have an affinity for the receptors that are of orders of magnitude greater than acetylcholine. They are composed of four proteins (2α, β, δ, γ) that form a pore in the cell membrane, each receptor having two α subunits that may be a homo or heteromeric (identical α subunits or a combination of distinct α subunits), which influences the pharmacology of the whole receptor because acetylcholine and neurotoxin bind to the α subunit. Ten distinct α subunits and three β subunits have been identified. Of these, $\alpha 1$ and $\beta 1$ are considered to be muscle specific subunits.[22] Thirdly, the target cells are afferent neurons associated with nociception though NAchRs are present in a variety of cells. Notwithstanding, it is expected that several inconsistencies will remain that could provide guidance on future laboratory investigations.

The cholinergic system in both the central and peripheral nervous systems has emerged as arguably the key system in the

perception and control of pain. Numerous pharmaceuticals and peptides with known analgesic activity act directly on these receptors. Within the cholinergic system nicotinic and muscarinic receptors not only contribute to modulating pain signals but also inflammation and consequently inflammatory pain. Within NAchR subtypes, homomeric α7, α4, and more recently α9 are key components while within the muscarinic subtypes, M3 is reportedly the leading component in pain modulation. Pain is experienced through specialized sensory neurons in the peripheral nervous system, and these neurons are part of the autonomic system. The sensation of pain may be caused by cells that secrete acetylcholine that are not part of the nervous system.

Under normal circumstances, the venom neurotoxins are injected by the cobra in relatively huge quantities, from 50 mg to 100 mg. Death by respiratory paralysis in rodents occurs in less than 5 minutes (see section on toxicology). At nonlethal doses, cobra venom from *N kaouthia* was recently reported to ameliorate adjuvant-induced arthritis in rats,[23] not only reducing pain but also reducing tissue damage, confirming it as a potential disease modifying antirheumatic drug and validating its use for the treatment of arthritis in Ayurvedic medicine. Cobra venom contains several peptides that exert analgesic and antiinflammatory activity in numerous animal models (Table 2).

COTX and CATX have been studied most, both neurotoxins being antagonists of the muscle–type α1 nicotinic receptor while CATX has also been established to be an antagonist of α7, α8, and α9 receptors.[22] Characteristically, the onset of pharmacodynamic activity of peripherally administered cobra toxins is realized only after several hours in contrast to aspirin and morphine but the activity is more prolonged.[24,25] This is consistent with the activity of whole cobra venom in similar models.[26] Central administration of both CATX and COTX gives rapid analgesic effects.[25,27] CATX that has been detoxified retains analgesic activity though significantly weaker than the native toxin,[28] confirming the relationship between affinity (as measured by NAchR binding) and efficacy.

The central analgesic effect of CATX was found to be superior to morphine at comparatively minute doses.[29] Additionally, it was found that the activity of these neurotoxins was opioid receptor independent.[24,25] Constant administrations orally or by injection of small dosage of cobra neurotoxins increase the leu-enkephalin content in hypothalamus, striatum, and midbrain and increase the met-enkephalin content in hypothalamus and midbrain, especially thalamencephalon.[30] CATX was recently confirmed to have antiinflammatory effects in the rat formalin and adjuvant arthritis models. CATX exhibited a dose-dependent analgesic action during Phase 1 and Phase 2 cycles in the formalin model (Qin, Soochow University, unpublished data). In this model, formalin increased the number of c-Fos-positive cells in the L4-5 spinal dorsal horn. Peripheral treatment with CATX inhibited formalin-induced increases in c-Fos-positive cells, atropine (5 mg/kg) antagonized the antinociceptive activity and canceled the inhibitory effect of CATX on c-Fos expression. This data supports the contention that CATX can exert antinociceptive effects through central pathways by direct or indirect activity via the dorsal root ganglion and that atropine acts between those two anatomical points. CATX also induced changes in the expression of Th1 inflammatory cytokines and upregulated the expression of the Th2 cytokine IL-10, thereby establishing dual mechanistic pathways for analgesic and antiinflammatory activity,[31] similar to the effects of whole cobra venom.[23] Of greater significance was the fact that CATX's antiinflammatory activity was inhibited by methyllyaconitine (MLA), an α7-specific antagonist.[31] Najanalgesin, a newly isolated peptide neurotoxin from cobras with homology to cardiotoxins, displayed analgesic activity with similar pharmacodynamics to the nicotinic antagonists, with slow onset, prolonged activity and antagonism by atropine.[32] Following the screening of *N atra* venom for analgesic peptides, a novel small molecular weight peptide of 1213 Da with analgesic activity has been reported, the LD_{50} of the intravenous injection of mice is 1.9875 mg/kg. These results showed that this peptide, NTXI, could strikingly increase the pain threshold of mice

TABLE 2 Analgesic Peptides From *Naja* Venoms Studied in Pain Models*

			Animal Models					
Peptide	**Source**	**Pharmacodynamic activity**	**Hot plate**	**Writhing**	**Tail flick**	**Adjuvant arthritis**	**Neuropathic**	**Formalin**
Cobra venom	*Naja kaouthia*	Multiple			+	+		
Cobrotoxin	*Naja atra*	a1 NAchR antagonist	+	+	+	+		
Cobratoxin	*Naja kaouthia*	a1, 7, 8, 9 NAchR antagonist	+	+	+	+		+
Najanalgesin	*Naja atra*	Not reported	+	+				
NTX1	*Naja atra*	Not reported	+					
Cobra venom Factor	*Naja kaouthia*	Antiinflammatory/ compliment depleting					+	

*NAchR indicates nicotinic acetylcholine receptor.

in the hot plate assay. Intraperitoneal injection of 0.2 mg/kg of NTXI could increase pain threshold from 100% to 184.35% in mice on the hot plate's threshold. The onset of the analgesic effect was slow, starting 2 hours after treatment and reaching its maximal effect after 4 hours.[33] In addition to neurotoxins, it should be noted that cobra venom factor also modulates the immune system through the complement cascade and has been reported to be effective in neuropathic pain models, which confirmed the importance of the immune system in the neuropathic pain process.[34]

By examining the receptors targeted by the venom's neurotoxin ligands, it should be feasible to isolate mechanistic pathways. It has been firmly established that α7 NAchRs are involved in the inflammatory pathway. Activation and inactivation of α7 subtypes can downregulate the inflammatory response. On the vagus nerve, activation of α7 subtypes downregulates inflammation.[35] In some cells, their activation triggers the expression of cyclooxygenase (COX2) enzymes,[36] the target of such drugs as aspirin and celecoxib (Celebrex). Alpha7 NAchR activation and COX2 also promotes tumor invasiveness.[36,37] Bungarotoxin, a CATX homologue, blocked COX2 expression and cell proliferation induced by 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) a derivative of nicotine but not by nicotine or N'-nitrosonornicotine (NNN) suggesting the involvement of more than one NAchR subtype.[36,38] NNN activity was inhibited by the α7 antagonist, MLA[38] apparently confirming the presence of both α1 and α7 mediated channels in these cells.[39,40] CATX can inhibit the proliferation of several tumors types,[41] which is attributed to the inhibition of α7 subtypes though it most likely includes α1 subtypes because COTX induces apoptosis in tumor cell lines too.[42] In one non–small cell lung cancer (NSCLC) line studied, mRNA and protein for a muscle-type α1 receptor was detected.[39,40] Although, mRNA for the α7 nAChR subunit was observed in all cell lines, α7 protein was not detectable by immunoblot in NSCLC cell extracts.[40] Interestingly, while CATX is a potent antagonist of the homomeric α7 NAchR, it was confirmed that its antiinflammatory activity was not mediated through this receptor because its activity could be antagonized by MLA. These observations confuse the current simple position that activation of the alpha7 receptor is important for antiinflammatory activity. MLA can block the production of COX2 implying that α7 homomers/heteromers interplay to orchestrate the immune/inflammatory response. It is often assumed that inhibition of nicotinic receptors by CATX or Bungarotoxin presumes the involvement of α7 subtypes, and this is clearly erroneous. The available information indicates that the antiinflammatory or analgesic activity of CATX is not mediated through α7 subtypes but likely through an α9 or even possibly an α1 heteromer.

The α1 heteromer hypothesis is supported by the fact that it is not solely expressed in muscle cells,[43] for that matter α7 receptors are not solely neuronal.[44,45] It has been established that fluoxetine (Prozac), sertraline (Zoloft), paroxetine (Paxil), nefazodone (Serzone), and venlafaxine (Effexor) block the activity of α1 and α3 NAChR in the low to intermediate μM range by noncompetitive inhibition of NAchR function,[46] drugs that may be used for adjuvant pain therapy. Cobra neurotoxins have very low affinity for α3 receptors, which are a target for drugs like bupropion (Zyban) and associated with addiction to nicotine. COTX, a classic α1 NAchR antagonist, also exerts analgesic activity by peripheral and central administration[23,26] similar in potency to CATX. Crotoxin (CrTX), the 24-kDa neurotoxin isolated from the venom of *Crotalus durissus terrificus*, like COTX binds primarily to the α1 NAchR and induces analgesia by central and peripheral administration.[47,48] It too has demonstrated analgesic effects in a number of animal models, and unlike the cobra neurotoxins, it has been found to be synergistic with aspirin, suggesting its target is not the α7 nor α9 NAchR subtypes. Like cobra neurotoxins, the analgesic effect of CrTX is slow to develop. In a model of neuropathic pain, the antinociceptive effect of CrTX was long lasting; it persisted for 64 days, long after it would have been excreted.[49] The effect of CrTX was mediated by the activation of central muscarinic receptors and partially, by activation of alpha-adrenoceptors and 5-HT receptors as reported for CATX.[24] Like CATX, Crotoxin is highly toxic to tumor cells,[50] suggesting the expression of a non-neuronal NAchR receptor. In light of the potential activity of antidepressants on NAchRs and the involvement of the serotonergic system in CATX and CrTX analgesia, it is interesting to note that cobra venom therapy was clinically associated with antidepressant effects[51-53] that might have been due solely to the relief of pain while CrTX-induced anxiolytic effects in spite of relieving pain.[54] The evidence that α1 NAchR antagonists are potent analgesics, promoters of neuronal survival that possess antitumor activity especially by central administration, leads to the conclusion that an alternative receptor should be considered as the primary target for antinociception produced by cobra neurotoxins.

Another peripherally located receptor that fits this requirement would be the α9 NAchR, a widespread receptor outside the central nervous system (CNS) that has recently been implicated in nociception[55,56] in addition to being present on lymphocytes, thereby having a potential role in immune modulation.[57] The activity of the highly specific α9 *Conus* antagonist, RgIA, exerts analgesic activity and immune modulation in the chronic constriction injury model of pain,[56] pharmacological properties exerted by CATX. The α9 receptor is also surprisingly antagonized directly by morphine[58] and both morphine and fentanyl disrupt cholinergic neurotransmission in the CNS,[59] which confirms a role for this receptor in the perception of pain and possibly opiate withdrawal. Interestingly, the chronic administration of nicotine, which desensitizes NAchRs, inhibits the development of tolerance and withdrawal symptoms to morphine in mice,[60] a characteristic associated with cobra venom therapy and neurotoxins.[30]

An alternative possibility is that CATX exerts its analgesic activity in vivo not only via a different NAchR subtype but actually through a different receptor such as P2X, an adenosine-5'-triphosphate (ATP) receptor involved in pain perception and now reported to be potently antagonized by alpha-bungarotoxin and MLA.[61] Functional homomeric (P2X[3]) and heteromeric (P2X[2/3]) receptors are highly localized on primary sensory afferent neurons that transmit nociceptive sensory information. Activation of these P2X(3)-containing channels may provide a

specific mechanism whereby ATP, released via synaptic transmission or by cellular injury, elicits pain particularly through the P2X(3) receptor.[62] It is expressed selectively at high levels in nociceptive sensory neurons, where it forms functional receptors on its own and in combination with the P2X(2) receptor: a location accessible to cobra toxins. Recent reports show that P2X(3) receptors are involved in chronic inflammatory and neuropathic pain.[63] The affinity of CATX, CrTX and COTX for other NAchRs and ATP receptors should therefore be reexamined in order to provide a clearer understanding of their potential analgesic pathways.

The involvement of muscarinic receptors in the activity of cobra toxins has been established. Scopolamine, a muscarinic antagonist, induces migraine headaches,[64] a known side effect of cobra venom therapy. Muscarinic antagonists have been isolated from cobra venom with a high affinity for the M5[65] and M3[66] receptor subtypes. It was recently reported that muscarinic receptor activated α7 nicotinic receptors inducing an antiinflammatory response.[67] This activity was also blocked by MLA and known to block the antiinflammatory activity of CATX. Morphine-induced antinociception was significantly inhibited by atropine in a dose-dependent manner,[68] which also antagonizes the antinociceptive activity of CATX[25] and gabapentin formulations.[69] It can therefore be assumed that the activity of morphine and CATX are ultimately controlled by muscarinic receptors in addition to the possible direct action of cobra muscarinic toxins at other muscarinic sites.

The difference in the speed of onset of analgesia between these pharmaceutical and biological agents may be attributed to morphine readily gaining access to central neurons. Cobra toxins most likely mediate the bulk of their activity from the periphery, though slow permeation into the CNS may occur. Interestingly the side-effect profiles of these cobra venom constituents in clinical studies may help indicate which receptors are being targeted.

PSYCHOLOGICAL STUDIES

Following the demonstration that cobra venom had antipyretic effects in guinea pigs, it was concluded that the venom was active at sites in the CNS—in this case, the thermoregulatory center. This led to studies in rats trained to run a circular maze, a technique employed previously to assess the central effects of other drugs. The rats were trained to negotiate the maze to the center to obtain a treat without error. It was noted that the effects of cobra venom elicited responses similar to those of opium alkaloids. The injection of small doses of cobra venom (0.005 mg) caused a stimulating effect increasing the speed at which the rat completed the maze. Increasing the cobra venom dose to 0.03 mg caused the animal fail completing the test.[70]

DRUG INTERACTION STUDIES

It was determined by Macht that the analgesia produced by cobra venom injections was due to its sedative effect on the brain. Previous research revealed that at appropriate levels, the venom antagonized to some extent the epileptiform convulsions produced by camphor.[9] An extensive investigation was carried out on a series of drugs and chemicals that in suitable doses produce convulsions of different physiological types. The effects of camphor, borneol, cocaine, atropine, nikethamide (Coramine), pentylenetetrazol (Metrazol), picrotoxin, phenol, absinthe, and caffeine on mice were thus investigated.[71] The action of some of these drugs was found to be antagonized or neutralized by subsequent injections of cobra venom. In still other cases, however, synergistic phenomena resulted from administration of cobra venom after the other drug. No synergism between cobra venom, on the one hand, and strychnine or phenol, on the other, was noted. Cocaine and cobra venom were usually synergistic, effecting greater toxicity. Absinthe and picrotoxin convulsions were definitely counteracted or much weakened by cobra venom injections. It was concluded that this data supported the view that cobra venom in suitable doses depresses the higher regions and synapses of the central nervous system, acting on both the cerebrum and medulla.

In separate studies, the ability of neurotoxins to substitute for morphine was studied on an analgesic model. In contrast to morphine, constant administration of neurotoxins orally or by injection in mice resulted in no decline in analgesic effect. Injecting cobra neurotoxins into addicted and tolerant rats increased their pain thresholds by 30% to 40%, suggesting that cobra venom can substitute for morphine. The toxic effects of cobra venom and morphine were also found to be cumulative.[30]

DRUG ADDICTION STUDIES

As noted above, COTX can substitute for morphine in animals that are addicted and tolerant of its effects. Repeated doses of cobra venom were assayed for its ability to induce habituation in comparison to morphine.[72] The study was conducted by examining the behaviors of rats in the Watson maze. While habituation and tolerance were readily demonstrated with the administration of morphine, such effects were absent using cobra venom.

In further studies on the application of cobra venom to controlling addiction, studies based on the naloxone-induced mouse jumping model, the results demonstrate that the numbers of jumping mice in the group to which snake venoms were administered both orally or by injection were much lower than those of groups to which only saline was administered.[30] In the addicted rat model with peripheral abstinence syndromes (vomiting, body twisting, salivation, and shaking), rats undergo an obvious change when treated with cobra venom, but the central syndromes (fighting, hair erection, and tear shedding) do not significantly change. The use of snake venoms to substitute for opiate drugs did not result in addiction.[30]

TOXICITY STUDIES WITH COBRA VENOM AND ITS NEUROTOXINS

It is well known that cobra venom is, in fact, potently toxic so it is worthwhile to review the currently known toxicology of cobra venom and its primary neurotoxins. Cobras do cause an

average of 50 000 deaths annually, which has motivated extensive research over the last 2 centuries in an effort to understand the mechanism of that toxicity.

Empirical studies on the acute toxicity of cobra venom have been conducted in several species of animals. Calmette[73] along with other investigators established by injection the toxic dose of cobra venom in several species of mammals (Table 3).

Prior to the 1930s, it was generally known that cobra venom was primarily neurotoxic, inducing paralysis similar to curare, with respiratory paralysis being the cause of death. Intubation of an animal injected with low doses of venom was life saving but not if large doses were administered.[74] The heart was last to be affected and could continue to beat for several minutes following the cessation of respiration. Lamb and Hunter had established in monkeys that injection of the venom destroyed motor neurons that may have underwritten the paralytic effects and that components of the venom could in fact access the CNS if they were given sufficient time to penetrate.[75] This could explain the lethal effects of the venom in spite of intubation.

It was also known that cobra venom was poorly hemolytic in contrast to viper venoms and that intravenous administration was far more toxic than subcutaneous or intramuscular injection. The injection of cobra venom at doses of 1mg/kg and above was associated with lethal outcomes in most species with rabbits, dogs, and horses being noted as quite sensitive to cobra venom relative to other species. Early administration of antivenom prevents respiratory paralysis after elapid snakebite. Victims with evidence of respiratory insufficiency after neurotoxic venom poisoning require rapid intubation and artificial ventilation.[76] Ventilatory care is easy to institute and is life saving. No cardiac, renal, or coagulation disorders were associated with the muscle paralysis after cobra envenomation.[77]

With further review of the available literature, it is possible to construct a preclinical toxicity profile of the venom. As the venom was originally selected for its neurotoxic properties, emphasis has been placed on data relating to that activity. Macht commenced with assays conducted in mice, rats, guinea pigs, rabbits, cats, and dogs using a standard potency of 1 mouse unit (MU) or approximately

TABLE 3 Acute Toxicity Tests Conducted With Cobra Venom In Vivo*

Species	Route	Dose mg/kg	LD 50 mg/kg	NOEL mg/mL	Observations
Mouse	Orally	50	ND	ND	No toxicity observed
	SC	0.075	ND	ND	Minimum lethal dose in 24 h
	IV	0.2	ND	ND	Toxic, survived >30 min
	SC	1	ND	ND	Pharmacokinetic, toxic
	SC	0.2	0.2	ND	
	IP	0.5-5.0	0.7-2.0	<0.5	Geographical variation
Rat	SC	0.66	ND	ND	Minimum lethal dose in 24 h
	NR	0.02-0.12	ND	>0.12	Psychological changes
	IP	0.08	ND	>0.08	No toxicity, organs normal
Guinea pig	SC	0.4	ND	ND	Minimum lethal dose in 24 h
	NR	0.1	ND	>0.1	Lowers temperature
Rabbit	SC	0.5	ND	ND	Minimum lethal dose in 24 h
	IV	0.025	ND	>0.025	No change in kidney function
	IV	1	ND	ND	Death in 25 min
Cat	IV	1.04	ND	ND	Lethal dose
Dog	Orally	15	ND	ND	No toxicity observed
	SC	0.8	ND	ND	Minimum lethal dose in 24 h
	IV	1.6	<1.6	ND	Toxic
	IV	0.5 CM Fr1	<0.5	ND	EEG activity ceases
	IV	0.5 CM Fr2	<0.5	ND	Respiratory paralysis 30-120 min
	IV	0.5 CM Fr3	<0.5	ND	Cardiovascular decline, BP drop
Horse	SC	0.05	ND	ND	Minimum lethal dose in 24 h

*LD indicates lethal dose; SC, subcutaneous; NOEL, no observable effect level; IV, intravenous; IP, intraperitoneal; ND, not done; NR, not reported; EEG, electroencephalogram; BP, blood pressure.

0.01 mg.[9] These experiments revealed that cobra venom first exerted a primary stimulating effect on both circulation and respiration. As the dose of venom increased, it was reported that the respiratory center in the medulla was slowly depressed and finally paralyzed. In the last stages of medullary paralysis, the toxic effect on the heart was noted, but death occured primarily through paralysis of the medulla, and the heart, as a rule, stopped shortly afterward. Similar effects were produced in experiments on cats and dogs. Vick et al fractionated cobra venom by cation exchange chromatography and assayed the effects of the fractioned peaks in dogs by electroencephalogram (EEG), electrocardiogram (ECG), and respiratory effects.[78] It was reported that injection of the neurotoxic fraction into dogs did not adversely affect EEG or cardiovascular parameters even with the onset of respiratory distress. Cobra cytotoxins, classically the cardiotoxins that comprise the highest fraction of the venom at about 30% to 40%, are basic amphipathic peptides of relatively weak lethal toxicity when administered intramuscularly (LD_{50} IM in mice is 52 mg/kg; in rats 65 mg/kg). They caused a reduction in blood pressure that ultimately interfered with polarization of the cardiac muscle causing arrest.[78] Bradycardia and hypotension postenvenomation are attributed to the increase in tumor necrosis factor levels in the blood.[79]

Direct administration of whole venom and neurotoxins to the brain induced convulsions identical to that of natural envenomation.[80] Interestingly, the activity of the venom and purified neurotoxin when applied to the brain exerted effects for over 8 hours, even after being washed out following a 30-minute exposure. However, with the prolongation of testing intervals, it was observed by Tseng et al that radioactive counts were increasing in the brain, which was supportive of the observations of Lamb and Hunter.[75] Vick et al had reported that cobra venom fractions impacted EEG performance.[78] A recent clinical report of a presumed cobra or krait envenomation reported symptoms similar to brain death,[81] suggesting that cobra venom components can in fact access the CNS, albeit slowly. Several studies with purified α-neurotoxins in the CNS of developing chick embryos have demonstrated that CATX can provide beneficial effects when applied directly to the CNS or administered to embryos by promoting neuronal survival.[82] It was established that for central protective activity, the neurotoxins must, oddly, have the ability to block muscle-type α1 nicotinic receptors.[83] However, there is no clear evidence in animals that cobra toxins can gain access to the CNS without direct administration.[84,85]

The cobra venom formulation used in early chronic toxicity studies did not simply employ dilutions of raw cobra venom. In the United States, cobra venom for injection, Nyloxin, was prepared originally by heating the venom up to 60°C for an unspecified period of time.[9] This was done to render the venom solution sterile. Reproduction of this method and heating up to periods of 3 hours should inactivate the enzymatic components of the venom; however, the cobra toxins retain >90% of their activity as measured by time-to-death studies in mice. Toxicological studies were conducted with Nyloxin in rats and rabbits to which repeated large and ultimately fatal doses were administered. Microscopic examinations of the internal organs revealed no pathologic changes. Prior to a clinical study by Hills and Firor, recordings of the changes in blood pressure and respiration of dogs following the intravenous injection of Nyloxin were made at the University of Maryland Medical School.[86] The material used contained 166 MU per cc (1.66 mg/mL). A pronounced depressor response was observed, and respiratory failure appeared to be the cause of death. Respiratory paralysis is the primary toxic effect of venom preparation. Chronic toxicology and biochemical studies with Nyloxin were conducted in rabbits[87,88] with daily injections ranging from 7 to 22 weeks. Kidney and liver functions of all animals were unaffected. There were also no changes in the morphology or chemistry of the blood. In subacute toxicity studies on rats given 2 MU (0.02 mg) of cobra venom intraperitoneally each day for 21 days showed no demonstrable effects on the blood elements or blood chemistry were produced. No histologic changes were detected in the livers, kidneys, brains, or pituitary glands.[86]

To assess the overt toxicity of raw cobra venom administered orally, a 28-day study was conducted in mice that were monitored for visible signs of toxicity and by weight (Receptopharm, unpublished data). No necropsies were conducted. The venom was solubilized at 1mg/mL in water, and the animals were permitted to drink the solution from their water bottles. The volume of water the mice consumed daily was recorded, and the average consumption was found to be 6 mL (6 mg) per day or 168 mg over the test period. No animal deaths were recorded, nor were there any signs of toxicity. The average weight gain of the animals was 4.87 g. At the end of the study, the venom solution was diluted in saline and 0.2 mg injected into the mice. Death occurred within 25 minutes, indicating that there was no immune protection nor had the venom deteriorated in solution during the study period. In mice, the minimum lethal dose by injection is reported to be 0.5 mg/kg (Receptopharm, unpublished data). The LD50 of native cobra venom by daily oral administration was greater than 300 mg/kg or 4000-fold higher than by injection. In dogs, stomach irrigation with native cobra venom at 0.5 mg/mL did not produce any adverse nor toxic effects for periods extending over 16 weeks, which would imply a poor uptake or modification of the toxic components.[89] In a series of studies on the oral toxicity of raw cobra venom in insects, it was found that only certain species of blowflies were susceptible to the venom by this route of administration. Interestingly, about 2% to 8% of the orally applied low molecular weight basic neurotoxin (Mr 7000) from cobra venom crossed the gut and was found in the insects' hemolymph.[90-92] The analgesic activity of Nyloxin delivered using a stomach tube to rats was absent.[93]

The question remains: Can orally administered venoms or toxins be effective? Are they not degraded in the stomach? Botulinum is the classic orally toxic peptide that survives digestion by associating with other proteins. The adsorption and activity of orally administered rattlesnake venom has been documented.[94-96] It has been clearly demonstrated that fragmented or denatured neurotoxins have biological activity in a variety of assays: binding receptors,[97] immunomodulatory activity,[98] and analgesic activity.[28] Fragmentation of the neurotoxic peptides

would certainly explain that absence of toxic effects by oral administration, though additional studies are warranted.

PHARMACOKINETICS

The pharmacokinetic profiles of labeled cobra venoms and their alpha neurotoxins were determined following rapid intravenous injection into rabbits.[85] The data obtained suggested a new three-compartment open pharmacokinetic model comprised of blood, a rapidly equilibrating "shallow" tissue compartment, and a slowly equilibrating "deep" tissue compartment. The overall elimination half-lives ranged from 15 to 29 hours, indicating a slow body elimination. Peak deep tissue concentration was reached at 4 hours for *N nivea* (Cape cobra) and *N haje* (Egyptian cobra) venoms and their toxins, suggesting that the sites of action of the venoms were located in the deep tissue compartment since most of the pharmacological, biochemical, and electrocardiographic effects of the venoms started 30 to 60 minutes after intravenous injection. The mean residence time in the body ranged from 20.8 to 51.8 hours, which correlated well with the findings of other authors for similar peptides[84,99] and the long duration of the pharmacological and biochemical effects induced by the venoms. The tissue distribution of the venoms and toxins was similar, with the highest uptake being in the kidneys, followed by the stomach, lungs, liver, spleen, intestine, heart, and diaphragm. The neurotoxins did not accumulate in any specific tissue, save for the kidneys during elimination. Data from Miller et al indicates that while there is little breakdown of the neurotoxin peptides as they circulate, the kidneys were the primary route of elimination and peptide degradation appeared to occur in the bladder.[99]

Of particular interest was a report by Ismail et al of high radioactivity in the stomach contents of animals injected with cobra venom,[85] which reached values higher than the kidneys, though this observation was not reported by Tseng et al.[84] Cobra venom has been employed to transiently alter the permeation of the stomach mucosa by direct application where it was proposed that unknown venom constituents opened the tight junctions between the epithelial cells which would then leak plasma and interstitial fluids[89] supporting the observations of Ismail et al.[85] Presumably, these tight junctions could conversely allow the entry of small cobra venom peptides when administered by mouth. Notably the plasma shedding induced by cobra venom could be blocked using azathioprine and prednisolone, pointing to an immune mediated interaction.

CLINICAL EXPERIENCE

According to Clarkes's *Materia Medica*, homeopathic cobra venom preparations are indicated for angina faucium, angina pectoris, asthma, dysmenia, hayfever, grief, afflictions of the heart, headache, striction of the oesophagus, pain in ovaries, plague, spinal irritation, and sore throat,[11] for the most part painful conditions. Cobra venom's "proving" (a rudimentary Phase I study with healthy volunteers using oral administration) was undertaken in 1853 with additional experiences being contributed by others.[10] Historically the application of cobra venom employed the oral route of administration ranging in potency from raw venom to 10^{-60} dilution.[10,100] Dilutions or triturations at 10^{-9} and above were without detectable effect.[10] The preferred oral dose of cobra venom was a dilution at 10^{-4} with the inclination to use less dilute solutions for increased response,[101] a contradiction of current homeopathic convention. Some investigators felt the venom was more potent if administered by injection not actually as an antibacterial agent but especially for cases of shock associated with typhoid and plague.

The estimated human lethal dose by injection was 15 mg.[102] When applied to the eye, vagina, or urethra, the venom induced acute inflammation but when adsorbed by the digestive tract, it mostly produced no ill effects.[73,74] In human envenomation, the heart could sometimes beat for as long as 2 hours following the cessation of respiration.[73] Numerous clinical studies have been conducted with cobra venom and purified cobra neurotoxins primarily for analgesic indications being administered orally and by injection, though the referenced studies are certainly not complete. From the 1930s onward, the venom was delivered clinically by parenteral injection, necessitating the production of a sterile biological solution. Studies in the United States were conducted with Nyloxin; studies in other territories may have used native venom preserved with phenol.[102] Only in China was cobra venom administered orally in manner similar to homeopathic methods, although the venom was undiluted. Deliberately excluded from this compilation are studies conducted with detoxified venoms and neurotoxins, which are reviewed elsewhere.[103] All of these studies would be considered allopathic in nature and not homeopathic, though it is very difficult to draw a clear distinction, save for the absence of succussion steps in the production of allopathic products. It should be noted that succussion has no impact on the toxicity of cobra venom at dilutions less than 10^{-6}. Doses of up to 0.55 mg/kg have been administered orally to humans without serious adverse effects. The dominant side effect has been headache. The ability of the venom to permeate mucosal membranes may explain the unpleasant esophageal effects that were described when the venom was taken orally. It is believed gastrointestinal disturbances reported in "provings" may also have resulted from bacterial contamination of the venoms.[104] Gram-negative bacteria are rarely isolated from cobra venom, but large counts of gram-positive organisms including staphlococci, clostridium, and mostly, enterococci are observed (Receptopharm, unpublished data).

Phase I Studies

Macht reported the first detailed descriptions of clinical studies in normal individuals that focused on the ability of Nyloxin to induce an analgesic effect (Table 4). No adverse events were reported. Subsequent studies were conducted in normal individuals to assess the impact of Nyloxin on vision, hearing, and psychological effects.[9,88,105] In these studies, the effects of cobra venom were compared primarily to morphine. Cobra venom enhanced the various faculties of vision, hearing, smell, and cognitive function without any reports of adverse events. Blood and biochemical tests were also reported as normal.[88]

Phase II Studies

Numerous studies to assess the effects of Nyloxin and other cobra venom formulations have been conducted in humans presenting with a variety of conditions. These studies are broken down into familiar formats to aid the reader (Tables 5-10). In most cases, limited toxicity was observed in the clinical studies with parenteral cobra venom, presumably due to the low doses employed. Toxic effects were dose related. At doses of 600 MU or 6 mg (0.085 mg/kg) side effects included nausea, vomiting, dry mouth, dizziness, sweating, headache, palpitations, diplopia, nystagmus, and hemiplegia. The estimated maximum tolerated dose by injection was 4 mg (0.061 mg/kg).

Three studies were placebo controlled (Table 5), though most were either open labeled (Table 6) or studies in which participants were experiencing difficulties with their current analgesic program (Table 7). The vast majority of treated patients were

TABLE 4 Safety Studies (Phase I) With Cobra Venom

Year	Reference	Ref no.	Application	No. of Participants	Dose	Duration	Response	Side Effects
1936	Macht	9	Analgesic effects	10	0.004-0.01 mg	Single	>60%	None reported
1939	Macht and Macht	105	Vision testing	12	0.05 mg	Single	>90%	Stimulation
1939	Macht and Macht*	106	Auditory tests	N/A	N/A	N/A	N/A	None reported
1939	Macht and Macht*	107	Cognitive functions tests	20	N/A	N/A	N/A	Stimulates like caffeine
1940	Macht and Macht*	108	Olfactory studies	N/A	N/A	N/A	N/A	Stimulation
1940	Hayman and Macht*	109	Biochemical studies	N/A	N/A	N/A	N/A	None reported

*References not accessible to author, provided as a convenience.

TABLE 5 Placebo-controlled Studies Conducted With Cobra Venom

Year	Reference	Ref no.	Application	No. of Participants	Dose	Duration	Response	Side Effects
1940	Steinbrocker et al	110	Arthralgias and related conditions	65	0.1 mg	10 d	40%	Injection site reactions
1954	Lumpkin and Firor	111	Arthritis	66	0.01-0.03 mg	4 mo	87%	2 allergic
1957	Meiselas and Schlecker	112	Osteoarthritis	14	0.01-0.03 mg	6 mo	0%	None reported

TABLE 6 Open Label Trials With Cobra Venom*

Year	Reference	Ref no.	Application	No. of Participants	Dose	Duration	Response	Side Effects
1938	Gayle and Williams	113	Parkinson's disease pain	18	0.05 mg	10 d	67%	None reported
1938	Chopra and Chowdan	114	Leprosy neuropathy	32	0.05-1.0 mg	2 mo	90%	None reported
1940	Chopra and Chowdan	102	Various pains	65	0.01-2.0 mg	2 wk	70%	None reported
1954	Bryson	53	Arthritis	466	0.01-0.03 mg	>1 y	82%	None reported
1954	Oaks and Quinn	115	Ocular therapy and headache	8	0.05 mg	2 y	NR	Allergic reactions
1975	Bechner and Idsvoog	116	Chronic pain	NR	NR	NR	10%	Injection site reactions
1993	Zhou et al	117	Stroke	96	0.6-1.3 mg	7-10 d	NR	NR
1997	Zhu et al	118	Diabetes complications	10	3 capsules/d	3 mo	98%	None reported
1999	Wu and Wu	119	RA	126	2 capsules/d	3 mo	98%	None reported
2000	Wei and Huang	120	RA	25	0.1 mg	6 wk	92%	None reported
2001	Wu and Zu	121	Digestive system cancer	122	3 capsules/ thrice daily	30 d	92%	None reported
2007	Wei et al	122	Scapulohumeral periarthritis	80	0.1 mg	2 wk	95%	None reported

*Shaded studies denote oral administration of venom. NR indicates not reported.

cases with advanced cancer, known to require potent analgesic intervention, with numerous participants in US studies already receiving opiate/NSAID combinations. In general, the following clinical observations were made:

1. not a single case under the care of clinicians showed any serious toxic reaction after cobra venom injections;
2. doses as low as 1 µg were found to be effective;
3. when compared with the analgesia produced by morphine, the effects of cobra venom were found to supervene more slowly but proved to be more lasting;
4. little or no benefit was derived from the initial injections;
5. cobra venom did not bring about the addiction and other undesirable features associated with the injection of opiates and cocaine;
6. an analgesic action was noted in some of the most intractable conditions as, for instance, in malignant tumors of the jaw, spine, and pelvic bones;
7. a number of the patients treated were morphine addicts, for whom it was possible to reduce the amount of narcotics to a minimum by substituting cobra venom injections, and in a few instances, opiates were dispensed with temporarily; and
8. once relief of pain was noted, the dosage could be reduced in frequency, first to alternate days and later patients could be kept comfortable with one or two injections a week.

In this respect, cobra venom was strikingly different from morphine, which usually leads rapidly to habituation requiring increasingly frequent dosage. Of the 41 clinical studies referenced here, there was only one study to report that cobra venom

TABLE 7 Drug Substitution Studies With Cobra Venom Where Standard of Care Was Inadequate*

Year	Reference	Ref no.	Application	No. of Participants	Dose	Duration	Response	Side Effects
1936	Macht	9	Cancer pain/neuralgia	115	0.01-0.02 mg	NR	>90%	Nausea
1938	Macht	123	Cancer pain including neuralgias and arthritis	200	0.05 mg	NR	70%	None reported
1939	Rutherford	52	Cancer pain/cystitis	17	0.01-0.03 mg	4 mo	88%	None reported, 10 µg maintenance
1940	Black	51	Cancer pain	17	0.05 mg	30 d	70%	Nausea and vomiting
1940	Macht	124	Cancer pain	4	0.05 mg	Up to 4 mo	70%	None reported
			Zoster	8		1 wk	75%	None reported
			Radiation burns	2		Up to 2 wk	100%	None reported
			Tabes dorsalis	17		1 wk	60%	None reported
1952	Hills and Firor	86	Cancer pain/migraine	30	0.1-1.2 mg	30 d	Not reported	Diplopia/hemiplegia/ vomiting
1960	Williams	125	Trigeminal neuralgia	8	NR	6 wk	100%	None reported
1968	Singh and Srivastava	126	Asthma	30	0.05-0.25 mg	38 mo	100%	None reported
1991	Song	127	Lung adenocarcinoma	7	3 capsules thrice daily	5 y	N/A	>3 y survival

*Shaded studies denote oral administration of venom. NR indicates not reported.

TABLE 8 Comparative Clinical Investigations With Cobra Toxins*

Year	Reference	Ref no.	Application	No. of Subjects	Dose	Duration	Response	Side Effects	Comparator
1999	Wang et al	123	Postoperative pain	72	0.0011 mg/kg	Single	Relief 2x morphine	Dry mouth, nausea, dizziness	Morphine
2001	Xu et al	129	Postoperative pain	100	NR	1 d	>90%	Nausea, dizziness, sweating, hypodynamia, palpitation	Tramadol, ibuprofen
2002	Xu et al	130	Moderate to severe cancer pain	230	NR	7 d	>83%	Side effects similar to tramadol	Tramadol, ilbuprofen

*Shaded studies denote oral administration of venom. NR indicates not reported.

had no analgesic activity; however, no adverse events were reported.[112] A later study reported that the efficacy of cobra venom (Cobroxin, believed to be from Egyptian cobra venom) in subjects with chronic pain was in the range of 5% to 10%.[116] There were some reported changes in the production of Nyloxin that could have had an adverse effect.[88] Other US and foreign studies referred in manuscript references here were positive about the benefits of cobra venom. Consequently, 97% of clinical analgesic studies with cobra venom were overwhelmingly positive. Reasonably consistent responses were observed in conditions treated with cobra venom between the American, European, and Chinese studies.

In postoperative pain management, pure cobrotoxin (COTX) was compared to morphine, where it was found to act twice as long as morphine but with 150th the amount of drug on a per kg basis.[128] In one study, cobrotoxin was not as effective against cancer pain as had been previously reported for whole cobra venom,[134] suggesting that a combination of other neurotoxins and venom components may be required for maximal effect.

Recent studies suggest that cobra venom could be employed to control withdrawal symptoms in opiate addicts.[30] Two clinical studies have been reported without any clear indication as to their success (Table 10). By the 1930s, cobra venom had already been established as a potential solution to the problem of opium addiction when taken in the form of a pill,[138] though this application was not part of homeopathic practice. Later studies have found that subjects suspected of being addicted to the opiate analgesics were able to reduce their opiate intake when using cobra venom.[52]

In all but two studies, the administration of cobra venom for the control of pain was overwhelmingly positive, leading to speculation as to why its use was abandoned in American and European medicine. According to a preliminary report by the American Medical Association in 1940, there was insufficient evidence to include it as a New and Nonofficial Remedy.[139] The major objections included difficulty with dosing, frequent treatment failures, potential for intense pain upon injection, and its failure to replace morphine completely; there were significant concerns about the quality of the product.[139] It was noted that pain upon injection was not associated with the Nyloxin formulation. However, the report seems at odds with the observed efficacy of cobra venom in controlling pain that was consistently reported at 70%.

TABLE 9 Open-label Trials Conducted With Pure Cobra Toxin*

Year	Reference	Ref no.	Application	No. of Participants	Dose	Duration	Response	Side Effects
1978	Wenshaw State Derm Inst	131	Leprosy neuropathy	30	0.035 mg	NR	90%	None reported
1980	Pu	132	Headache	96	0.07 mg	10 d	81%	None reported
			Sciatica				100%	None reported
			Trigeminal neuralgia				81%	None reported
1980	Zeng	133	Sciatica	64	0.07 mg	NR	90%	None reported
			Low back pain				60%	None reported
			RA				70%	None reported
			Other; migraine, amputation, epilepsy				83%	None reported
1995	Cao et al	134	Cancer pain	NR	0.07 mg	NR	33%	None reported
			Trigeminal neuralgia				100%	None reported
			Sciatica				100%	None reported
			Low back pain				100%	None reported
1998	Gao	135	Sciatica	182	0.07 mg	20 d	89%	None reported
1999	Zhu et al	136	Acute and chronic pain	92	0.07 mg	5 d	>82%	Dry mouth, nausea, dizziness

*NR indicates not reported; RA, rheumatoid arthritis.

TABLE 10 Treatment of Opiate Addiction

Year	Reference	Ref no.	Application	No. of Participants	Dose	Duration	Response	Side Effects
1991	Li and Zhou	137	Opiate addiction	90	NR	NR	NR	Reduces withdrawal symptoms
1993	Xiong et al	30	Opiate addiction	300	NR	NR	NR	Not reported

*NR indicates not reported.

CONCLUSION

Cobra venom is classified as a homeopathic drug, though its usage has been more consistent with allopathic medicine. However, opium and morphine were considered homeopathic drugs in the United States, used at potencies as low as 3X, until they were subjected to prescription control under the Harrison Narcotics Tax Act of 1914.[11] The preclinical data obtained with cobra venom and its constituent neurotoxins from recent laboratory studies have simply confirmed many of the early clinical observations. The promiscuity of the nicotinic receptors for other drugs (opiates and antidepressants) supports some of the clinical responses in depression and addiction. Complicating the picture further is that cobra venom has several analgesic components that may interact to provide a concerted effect. More detailed investigations are desirable to better understand how cobra neurotoxins exert their analgesic effects, especially with regard to the drug's apparently central effects. It would also prove enlightening if a greater emphasis in laboratory studies was placed on determining a more detailed pharmacological profile of the NAchRs involved, thereby providing a clearer understanding of the mechanisms.

Today, opiate drugs, in spite of their shortcomings, remain the backbone of moderate to severe pain management in spite of significant efforts to find superior substitutes. Cobra venom is a readily available resource that is experiencing increased production and presents a useful resource in developing nations where potent and cost-effective analgesics are needed. Cobra venom's impressive safety record and observed response rate, in addition to the recent laboratory confirmations of cobra venom peptides' potential in analgesic models, may warrant its reintroduction as an alternative to opiates. The successful conduct of controlled clinical studies to modern standards would help support this proposal. Furthermore, the reported analgesic activity of cobra venom by oral administration is contrary to current dogma that needs validation at least in animal models.

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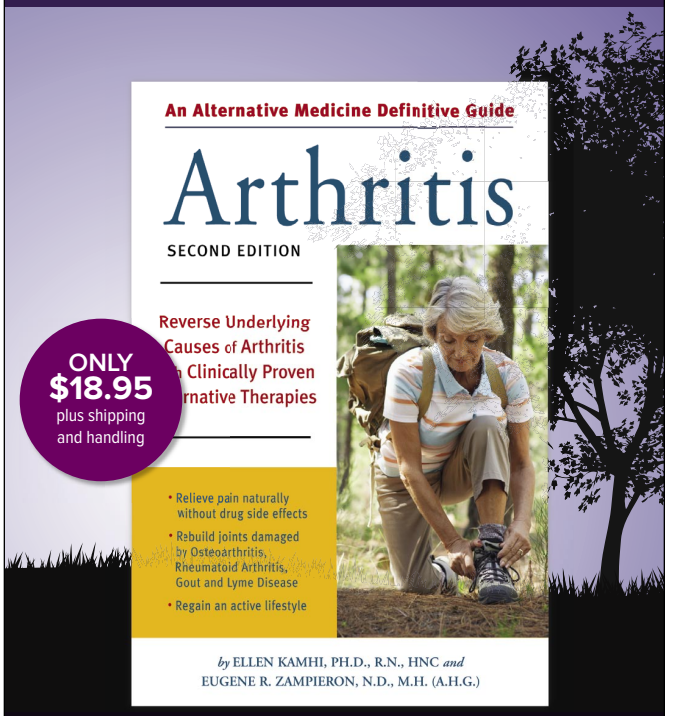

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