

# NYLOXIN

## Drug Insert

### DESCRIPTION

Nyloxin preparations are made from the venom of the Asian cobra *Naja tripudians*. They are homeopathic formulations that include oral, topical and sterile injectables for subcutaneous use.

**Active ingredient:** Cobra venom.

**Inactive ingredients:** Water, Sodium chloride, preservatives

### INDICATIONS

According to Clarke's Materia Medica, Nyloxin preparations are indicated as homeopathic medications for; angina faucium, angina pectoris, asthma, dysmenia (painful menses), hayfever, grief (depression), affections of the heart, headache (migraine), striction of the oesophagus, pain in ovaries (ovarian cysts), plague, spinal irritation (back pain) and sore throat.

Clinical experience shows that Nyloxin may also provide relief from other forms of pain.

### PHARMACOLOGIC CATEGORY

Anticholinergic.

### PHARMACOLOGY

The principal active components in the venoms are neurotoxins. These neurotoxins primarily target the cholinergic system by blocking the activity of acetylcholine, and compete with nicotine for receptor binding proving they are nicotinic antagonists. Nicotinic receptors are widespread throughout the body and are present on a variety of cells including nerve, immune and muscle. By targeting nicotinic receptors cobra venoms and cobra neurotoxins have recently been shown to have anti-inflammatory, antitumor and analgesic activity. The literature suggests that these activities are most likely mediated through 3 of the 10 known nicotinic receptors; alpha1, alpha7 and alpha9.

### PHARMACODYNAMICS

Characteristically, the onset of pharmacodynamic activity of peripherally administered cobra venom and cobra toxins is realized only after several hours in contrast to aspirin and morphine but the activity is more prolonged. In animal models Nyloxin does not induce tolerance nor addiction.

**Table 1: Analgesic peptides from cobra venom studied in animal models**

Peptide	Source	Pharmacodynamic Activity	Animals Models					
			Hot Plate	Writhing	Tail flick	Adjuvant Arthritis	Neuropathic	Formalin
Cobra venom	Naja kaouthia	Multiple			+	+		
Cobrotoxin	Naja atra	α1 NACHR antagonist	+	+			+	
Cobratxin	Naja kaouthia	α1,7,8,9 NACHR antagonist	+	+	+	+		+
Najanalgesin	Naja atra	Not reported		+	+			
NTXI	Naja atra	Not reported	+					
Cobra venom Factor	Naja kaouthia	anti-inflammatory/complement depleting						*

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. Cobratxin exhibited a dose-dependent analgesic action during Phase 1 and Phase 2 cycles in the formalin model. In this model formalin increased the number of c-Fos-positive cells in the L4-5 spinal dorsal horn. Peripheral treatment with Cobratxin inhibited formalin-induced increases in c-Fos-positive cells, atropine (5mg/Kg) antagonized the antinociceptive activity and canceled the inhibitory effect of Cobratxin on c-Fos expression. 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. NTXI, a small peptide, could strikingly increase the pain threshold of mice 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 2h after treatment reaching its maximal effect after 4 h. In addition to neurotoxins, it should be noted that cobra venom factor (CVF) 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.

Cobra venom was recently reported to ameliorate adjuvant-induced arthritis in rats not only reducing pain but also reducing tissue damage confirming it as a potential disease modifying anti-rheumatic drug. Native cobra venom therapy at two different doses showed a significant protection against adjuvant-induced arthritic changes in several symptoms such as paw weight, paw and ankle diameters. The restoration of urinary hydroxyproline by cobra venom treatment indicated that it inhibited collagen break down and thereby prevented the cartilage damage caused by disease induction. Cobra venom treatment also significantly restored urinary glucosamine level. In adjuvant induced arthritis the alteration of glycohydrolase activity in joints may increase excretory glucosamine level. Thus restoration in excretory glucosamine concentration by the administration of cobra venom may protect against cartilage degradation. In the present study it was found that the levels of IL-10 were decreased in arthritic animals and venom treatment significantly increased serum IL-10 level. Cobratxin was recently confirmed to have anti-inflammatory effects in the rat formalin and adjuvant arthritis models. Cobratxin also induced changes in the expression of Th1 inflammatory cytokines and up-regulating the expression of the Th2 cytokine IL-10 thereby establishing dual mechanistic pathways for analgesic and anti-inflammatory activity, similar to the effects of whole cobra venom. Cobratxin also appeared to protect joints from inflammatory damage. It has been reported that cobra venom also displayed anti-inflammatory activity in several

animal models such as Xylene induced ear edema in mice, rat air pouch model and carrageenan induced paw edema model.

Cobra venom contains small amounts of other peptides that block muscarinic receptors, calcium and voltage-activated potassium channels, inhibitors of the complement cascade in addition to nerve growth factors.

### CONTRAINDICATIONS

The effects of camphor, borneol, atropine, nikethamide (Coramine), pentylenetetrazol (Metrazol), picrotoxin, phenol, absinth, and caffeine *on mice* were found to be antagonized or neutralized by subsequent injections of cobra venom. Absinth and picrotoxin convulsions were definitely counteracted or much weakened by cobra venom injections. The toxic effects of cobra venom and morphine were also found to be additive. At higher doses Atropine blocks the analgesic activity of cobra neurotoxins.

Drugs or products with possible negative interactions include: nicotine, vitamin B12, azathioprine, and prior history of allergies to venoms.

### PRECAUTIONS

Cocaine and cobra venom were usually synergistic, effecting greater toxicity. The toxic effects of cobra venom and morphine were also found to be additive. Injecting cobra neurotoxins into addicted and tolerant rats increased their pain thresholds by 30-40% suggesting that they can substitute for morphine.

When adding cobra venom therapy to a current drug regime it should be noted that cobra venom: may have additive effects with opiates and may lower blood pressure.

Pregnancy: No significant data has been collected on the use of Nyloxin during pregnancy. No animal reproduction studies have been conducted to assess the effects of Nyloxin on the developing fetus.

Nursing mothers: It is not known whether this drug is distributed into breast milk. Oral administration of Nyloxin is not toxic though it may exert activity in infants.

Pediatric use: There is no information on the use of Nyloxin in children and young adults.

### INTERACTIONS

Cobra venom peptides can exert immunomodulatory effects. Exercise caution when administering similar drugs such as steroids.

Cobra venom had additive effects when administered to animals using opiate analgesics. No contraindications with aspirin have been observed in animal studies. INo adverse effects were reported when cobra venom was introduced into the analgesic regime using drug combinations of morphine, Demerol, procaine, pantopon, aspirin, phenacetin, codeine, and phenobarbital.

### ADVERSE REACTIONS

The majority of reported adverse effects to cobra venom are associated with the neurotoxic components of the venom.

In clinical studies with cobra venom subjects reported the following dose related adverse effects; headache, nausea, vomiting, dry mouth, dizziness, sweating, palpitations, diplopia, nystagmus, hemiplegia.

### SERIOUS ADVERSE REACTIONS

With the injection of Nyloxin allergic reactions, sometimes severe (anaphylactic), have been reported. Anaphylaxis is manifest usually within 30 minutes of administration. The use of antihistamines was found to alleviate the allergic reaction.

### FORMATS

Nyloxin is supplied in several formats. General prescribing guidance is provided for convenience. Always follow your health practitioner's instructions.

### DOSAGE AND ADMINISTRATION

In the reference text, *The Prescriber, A Dictionary of the New Therapeutics*, cobra venom is recommended at potencies ranging from 3X to 30X, with a frequency of hourly to daily. Potencies supplied by the manufacturer range from 4X to 8X. The text, *A Clinical Repertory to the Dictionary of Materia Medica*, should be consulted for specific treatment regimes.

It is important to note that there is a latent period of effect before the benefits of Nyloxin manifest themselves. A reduction in pain levels of 50% to 80% is expected. Once a positive effect has been attained the dose of Nyloxin may be reduced in frequency.

**TOPICAL** formulations of Nyloxin can be employed on an "as-needed" basis. Apply directly to the treatment site.

**ORAL** formulations of Nyloxin are dosed initially at 2 sprays every 4 to 6 hours. Dosing may be reduced when maximum pain reduction has been attained.

### PARENTERAL FORMULATIONS

Note: Always visually inspect bottles for particulate matter and discoloration prior to administration.

Nyloxin for injection is supplied as preserved 0.1mg/ml and 0.5mg/ml solutions. Initial dosing is 0.01mg (0.1ml) subcutaneously daily, which can then be elevated up to 1cc over the course of several days. The initial treatment period is 14 days. If an adequate response (pain reduced by 50%) has not been attained within 14 days a switch to the 0.5mg/ml formulation is recommended using the same dose escalation procedure. The maximum recommended dose of Nyloxin is 1mg/day.

### Maintenance Phase for parenteral formulations:

Clinical experience suggests that maintenance of effect can be accomplished by reducing the dose size and frequency. Progress should be monitored on a regular basis. With marked local injection site reactions (more than 2"/5cm in diameter) and/or temperature reactions above 100.4 °F (38 °C), co-administration of antihistamines (diphenhydramine) is recommended.

### STORAGE

Refrigerate injectables (2-10 °C / 36-50 °F) when not in use.

Topical and oral suspensions may be stored at ambient room temperature (15-27 °C / 65-80 °F) away from direct sunlight.

### STABILITY

Oral and topical Nyloxin is stable for 24 months at ambient temperatures.

Nyloxin for injection is stable for approximately 24 months when stored refrigerated.

### SAFETY INFORMATION

It is generally recognized that cobra venom taken by mouth is non-toxic even when administered at doses that far exceed the lethal dose when given by injection. 2.Large doses (130mg) of cobra venom administered orally to dogs gave no apparent signs of toxicity. Stomach irrigation with native cobra venom at 0.5mg/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.

#### Respiratory

The injection of cobra venom at 1mg/Kg and above is associated with lethal outcomes in most species. Respiratory paralysis in the primary toxic effect of venom and the means by which prey is killed. 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. Ventilatory care is easy to institute and is life saving.

#### Cardiovascular

Native cobra neurotoxins have no impact on the heart as determined by toxicity testing. No cardiac, renal or coagulation disorders were associated with the muscle paralysis after cobra envenomation.. It was reported that no neurotoxic fraction from cobra venom injected into dogs adversely affect EEG or cardiovascular parameters even with the onset of respiratory distress. There are pharmacologically distinct nAChRs are responsible for the differential effects of nicotine on heart rate however cobra neurotoxins are not ligands for these receptors.

#### Neurological

Numerous studies with alpha-neurotoxins in the CNS of developing chick embryos have demonstrated that Cobra toxins can provide beneficial effects when applied directly to the CNS. Embryos immobilized with neuromuscular blocking agents for differing periods of incubation had an increased number of motoneurons in the brachial and lumbar lateral motor columns. Limb muscles from embryos with excess motoneurons exhibited relatively normal differentiation and had acetylcholinesterase (AChE) stained endplates which were innervated. It was interesting to note that α1-type nicotinic acetylcholine receptor binding activity was required for neuronal protection, a pharmacological action clearly demonstrated for Cobra toxins.

#### Chronic toxicity studies with Nyloxin

In subacute toxicity studies on rats given 0.08mg/Kg of Nyloxin intraperitoneally each day for 21 days showed no demonstrable effects on the blood elements or blood chemistry were produced. No histologic changes detected in the livers, kidneys, brains, or pituitary glands.

Large doses of Nyloxin were injected into rabbits of periods extending from 2 to 21 weeks. The drug was administered daily for 5 days per weeks with dose of 0.05mg and 0.1mg per rabbits (actual human dose). The drug was administered by i.v. and i.m. routes. 3Even with doses reaching 9.9mg there were no change in blood chemistries or coagulation time. Studies conducted on the kidney and liver function of rabbits under the same protocol reveal no changes relative to normal. Microscopic examinations of the internal organs revealed no pathologic changes.

#### Pharmacokinetics

The pharmacokinetic profiles of labeled cobra venoms and their alpha neurotoxins were determined following rapid i.v. injection into rabbits. The data obtained suggested a new three-compartment open pharmacokinetic model comprising blood, a rapidly equilibrating 'shallow' tissue compartment and a slowly equilibrating 'deep' tissue compartment. The overall elimination half-lives ranged from 15 to 29 hr, 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 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 30-60 min after i.v. injection. The mean residence time in the body ranged from 20.8 to 51.8 hr, which correlated well with the findings of other authors for similar peptides 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 indicates that while there is little breakdown of the neurotoxin peptides while circulating, the kidneys were the primary route of elimination and peptide degradation appeared to occur in the bladder.

It was reported that high radioactivity was attained in the stomach contents of animals injected with cobra venom, which reached values higher than the kidneys. 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. 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.

#### Reproduction and Teratogenicity

Controlled reproduction studies with cobra venom have not been conducted. During the conduct of the chronic toxicity studies a rabbit became pregnant. The gestation was normal and delivery 3 normal offspring, 2 being reared by the female. One of the offspring was killed accidentally. This parental female received a total of 90 injections or 4.5mg of Nyloxin, 9 injections being intravenous.

No adverse effects were reported when treating pregnant women with 0.05mg doses (Bryson, 1954)

#### CLINICAL EXPERIENCE

Homeopathic medications are presumed to be safe as it is erroneously believed that the active components are used in such low levels that no possible danger could exist. Cobra venom was unusual in that it was used at relatively high concentrations and was "proved" (a rudimentary Phase I study) as raw venom. Cobra venom is a component of Chinese and Indian traditional medicine. There is literature on over 70 clinical studies conducted with cobra venom, much of it from China, the majority of studies having focused on the analgesic activity of the drug. In Asia, cobra venom is administered orally, either in a drink or in capsules, and by injection.

In the U.S., over 30 clinical studies were undertaken and published with parenteral Nyloxin that enrolled over 1000 subjects. They are listed and arranged below in tables by study type. The first detailed descriptions of clinical studies conducted with parenteral Nyloxin in normal individuals was reported by Macht where the studies focused on the ability of Nyloxin to induce an analgesic effect (Macht, 1936). No adverse events were reported (Table 2). Subsequently studies were conducted in normal subjects to assess the impact of Nyloxin on hearing, vision, smell, psychogalvanic reflexes and psychological effects (Macht and Macht, 1939; Macht and Macht, 1940). 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 in contrast to morphine. Blood and biochemical tests were also reported as normal (Hayman and Macht, 1940).

**Table 2: Phase I studies conducted with Nyloxin**

Year	Reference	Application	No. of Subjects	Dose	Duration	Response	Side effects
1936	Macht	Analgesic effects	10	0.004-0.01mg	single	>60%	none reported
1939	Macht & Macht	Vision testing	12	0.05mg	single	>90%	stimulation
1939	Macht & Macht	Auditory tests	12	0.05mg	n/a	n/a	none reported
1939	Macht & Macht	Cognitive functions tests	20	0.05mg	n/a	n/a	stimulates like caffeine
1940	Macht & Macht	Olfactory studies	n/a	0.05mg	n/a	n/a	stimulation
1940	Macht & Macht	Psychogalvanic reflexes	n/a	0.05mg	n/a	n/a	reduced response
1940	Hayman & Macht	Biochemical studies	n/a	0.05mg	n/a	n/a	none reported

n/a: not available.

Of the 22 clinical studies referenced here there was only one study to report that cobra venom had no analgesic activity, however no adverse events were reported (Meiselas et al., 1957). The Meiselas study was one of 3 placebo-controlled studies (Table 3). Steinbrocker et al (1940) reported a 40% response rate in placebo-controlled study. Lumpkin et al., (1952) reported a response rate of 87% using essentially the same formulation as Meiselas (1957).

**Table 3: Placebo controlled trials with Nyloxin**

Year	Reference	Application	No. of Subjects	Dose	Duration	Response	Side effects
1940	Steinbrocker et al	Arthralgias and related conditions	65	0.1mg	10 days	40%	injection site reactions
1954	Lumpkin et al	arthritis	66	0.01-0.03mg	4 months	87%	2 allergic
1954	Jackman	Neuroses	19	0.1-0.5mg	daily	70%	injection site reactions
1957	Meiselas et al	osteoarthritis	14	0.01-0.03mg	6 months	0%	none reported

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 5-10% (Bechner and Idsvoog, 1975). There were some reported changes in the production of Nyloxin that could have had an adverse effect on the product's performance (Table 4).

**Table 4: Open labeled studies with Nyloxin**

Year	Reference	Application	No. of Subjects	Dose	Duration	Response	Side effects
1937	Macht	Parkinsons disease pain	6	n/a	n/a	50%	None reported
1938	Gayle and Williams	Parkinsons disease pain	18	0.05mg	10 days	67%	none reported
1954	Bryson	arthritis	466	0.01-0.03mg	>1 year	82%	none reported
1954	Oaks and Quinn	Ocular therapy and	8	0.05mg	2 years	not reported	Allergic reactions
1975	Bechner and Idsvoog	Chronic pain	NR	NR	NR	10%	Allergic reactions

Several generalizations have been made with regard to the effects of cobra venom therapy, briefly summarized as follows: not a single case under the care of clinicians showed any serious toxic reaction after cobra venom injections; doses as low as 1 microgram were found to be effective; little or no benefit was derived from the initial injections; 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; 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 Bryson's large study in subjects with arthritis several general observations were made: there was an improvement in general health; lowering of abnormal blood pressure; relief from recurrent headaches; partial control of trigeminal neuralgia; and a general improvement in emotional outlook and reduced mental depression.

When compared with the analgesia produced by morphine, the effects of Nyloxin were found to superevne more slowly but proved to be more lasting. It 5did not bring about the addiction and other undesirable features associated with the injection of opiates and cocaine. It was reported by Rutherford (1939) that a number of the patients treated were morphine addicts where it was possible to reduce the amount of narcotics to a minimum by substituting cobra venom injections - in a few instances opiates were dispensed with temporarily. In this respect cobra venom was strikingly different from morphine which usually leads rapidly to habituation requiring increasingly frequent dosage. Recent studies suggest that cobra venom could be employed to control withdrawal symptoms in opiate addicts.

**Table 5: Drug substitution studies with Nyloxin where standard of care was inadequate.**

Year	Reference	Application	No. of Subjects	Dose	Duration	Response	Side effects
1938	Macht	Cancer pain/neuralgia	115	0.01-0.02mg	not reported	>90%	Nausea
1938	Macht	Cancer pain and various	200	0.05mg	not reported	70%	none reported
1939	Rutherford	Cancer pain/cystitis	17	0.01-0.03mg	4 months	88%	none reported, 10ug maintenance
1940	Black	Cancer pain	17	0.05mg	30 days	70%	Nausea and vomiting
1940	Macht	Cancer pain	4	0.05mg	up to 4 months	70%	None reported
		Zoster	8		1 weeks	75%	None reported
		Radiation burns	2		up to 2 weeks	100%	None reported
		Tabes dorsalis	17		1 week	60%	None reported
1947	Tan and Ives-Tan	Herpes zoster	5	n/a	n/a	n/a	n/a
1952	Hill & Firor	Cancer pain/migraine	30	0.1-1.2mg	30 days	not reported	diplopia/hemiplegia/vomiting
1960	Williams	trigeminal neuralgia	8	not reported	6 weeks	100%	None reported
1968	Singh and Srivastava	Asthma	30	0.05-0.25mg	38 months	100%	None reported
1991	Song	lung adenocarcinoma	7	not reported	5 years	n/a	7 w/ith greater than 3 years survival

Many foreign studies were positive on the benefits of cobra venom and reasonably consistent responses were observed in conditions treated with cobra venom between the American, European and Chinese studies though the venom formulations differed. Consequently 97% of clinical analgesic studies with cobra venom were overwhelmingly positive even with oral administration (Table 6)

**Table 6: Clinical studies with oral administration of cobra venom or cobra toxins**

Year	Reference	Application	No. of Subjects	Dose	Duration	Response	Side effects
1991	Song	Cobra/Viper venom	7	3 caps/Ld	5 years	Increased survival in 7	None reported
1997	Zhu et al	Cobra	10	3 caps daily	3 months	98%	None reported
1999	Wu and Wu	Cobra	126	NR	3 months	96%	None reported
2001	Wu and Zu	Cobra	122	3 caps/Ld	30 days	92%	None reported
2001	Xu et al	Cobrotoxin +	100	0.16	1 day	>90%	Nausea, dizziness, sweating, hypodynamic, palpitation
2002	Xu et al	Cobrotoxin +	230	0.16	7 days	>83%	Side effects similar to tramadol

In clinical use, cobra venom was used in controlling pain in a wide variety of indications as listed in Table 7. According to a preliminary report by the AMA in 1940, it was thought wise to exercise special case in subjects with psychic disturbances and severe diseases for the liver and kidneys.

**Table 7: Indications where cobra venom has been used to control pain.**

Neoplasms or tumors	Thrombo-angitis obliterans
Neuralgic deformations	Osteitis deformans
Tic douleureux	Eye conditions
Tabetic crises	Adhesions (intestinal etc.)
Arthritis	Torticolis
X-ray burns	Syringomyelia
Radium burns	Multiple sclerosis
Parkinson's disease	Epilepsy
Amputation stumps	Prostatic pain
Neurofibromas	Vesical pain
Herpes zoster	Dysmenorrhea
Leprosy (neuritic manifestations)	Pyelocystitis
Migraines	Sinus pain
Stenocardia	Pre-operative and postoperative
Raynaud's disease	analgesia
	Narcotic addiction

No exacerbation of cardiac, hypertensive or diabetic patients occurred nor was any abnormality in urinalysis reported.

#### Reported side effects.

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 6mg (0.085mg/Kg) side effects included nausea, vomiting, dry mouth, dizziness, sweating, headache, palpitations, diplopia, nystagmus, hemiplegia. It is expected that diplopia or nystagmus will be the first indicators of intoxication, an effect that is readily reversible and, in fact, quite a useful symptom. Subjects can readily determine the onset of such effects and relate them to the clinician. The estimated maximum tolerated dose (MTD) by injection was 4mg (0.061mg/Kg). For parenteral products, the most serious side effect is that would be expected in anaphylaxis. In prior studies controlling this reaction can be accomplished with antihistamines (Benadryl).

Oral formulations of cobra venom have a history of use under the auspices of homeopathic medicine but they were not studied with the intent of building a drug profile. It is generally accepted that cobra venom has no oral toxicity; however, it had been reported that large oral doses of cobra venom induce irritation to the throat that can be severe. The usual side effects with high doses (≥ 3.5mg) of cobra venom were headache, nausea, sore throat, allergic rhinitis and coughing. With lower venom doses (<0.35mg) a dry throat sensation is often reported that is transient.

Gastrointestinal upset was also reported though it is believed this stemmed from bacterial contamination found in raw venoms. Similar gastrointestinal symptoms have been reported by Chinese physicians. Current oral Nyloxin solutions have been sterile filtered and contain a preservative that meets USP requirements.

#### CLINICAL REFERENCES

- Bechner TF, Idsvoog P. Drug use and distribution in a pain rehabilitation center. Amer. J. Hosp. Pharm. 1975; 32:285-289
- Black WT. Cobra venom for the relief of pain. South. M. J. 1940; 33: 432
- Bryson KD. The treatment of chronic arthritis with a combination of cobra venom, formic acid, and silicic acid. Am Surg. 1954 Jul;20(7):751-5.
- Gayle, RF, and Williams, JN. Symptomatic treatment of Parkinsonism symptoms with cobra venom, South. M. J. 1938; 31: 188-192.
- Hayman M, Macht DI. Clinical and biochemical studies in cobra venom therapy. Med. Rec. 1940; 152: 67
- Hills RG, Firor WM. The use of more potent cobra venom for intractable pain. Am Surg. 1952 Sep;18(9):875-9.
- Jackman AI. Cobra venom therapy in the neuroses; a preliminary report. Dis Nerv Syst. 1954 Apr;15(4):99-102.
- Lumpkin WR, Firor WM. Evaluation of the Bryson treatment of arthritis. Am. Surgeon (1954); 20:756-759
- Macht DI. Experimental and Clinical Study of Cobra Venom as an Analgesic. Proc Natl Acad Sci U S A. 1936 Jan;22(1):61-71.
- Macht DI. Therapeutic experiences with Cobra venom. Ann. Int. Med. 1938; 11: 1824-1833.
- Macht DI and Macht MB. Effect of Cobra venom and opiates on vision, J. Exper. Physicol. 1939; 25:481
- Macht DI and Macht MB. Effects of cobra venom on hearing. Am. J. Physiol. 1939; 126:574
- Macht DI and Macht MB., Effects of cobra venom on cognition, Am. J. Physiol. 1939; 126:575
- Macht DI and Macht MB. Effect of cobra venom and the opium alkaloids on the psychogalvanic reflex, Am. J. Physiol. 1940; 129:412
- Macht DI and Macht MB. Comparison of the effect of cobra venom and opiates on olfactory sense, Am. J. Physiol. 1940; 129:411-412
- Macht DI, Cobra venom therapy in dermatology and syphilology. Urol and Cutan Rev. 1940; 44:119
- Macht DI. New developments in pharmacology and therapeutics of cobra venom. Tr. Am. Therap. Soc. 1940; 40
- Meiselas LE, Schlecker AA. The effect of Nyloxin on the pain of arthritis. N Y State J Med. 1957 Jun 15;57(12):2067-8.
- Oaks LW, Quinn JH. Cobra venom in ocular therapy. Trans Pac Coast Otophthalmol Soc Annu Meet. 1954 35:71-82.
- Preliminary Report of the Council, J.A.M.A. 1940; 115(14):1196-1197
- Rutherford RN. The Use of Cobra Venom in the Relief of Intractable Pain, NEJM 1939; 408-413
- Song YT. Clinical observation of snake venom on lung cancer. Clinical. 1991. 6: 311-312
- Steinbrocker O, McEachern GC, Camatta EP and Brooks F. Experience with cobra venom in Arthralgia and related conditions, JAMA 1940; 114:318
- Williams EY. Treatment of trigeminal neuralgia with cobra venom. J Natl Med Assoc. 1960 Sep;52:327-8.
- Wu YQ, Yu W. Clinical observation of capsule in the treatment of infertility group in 122 cases of the digestive system cancer. Journal of Snake, 2001. 13: 26-28
- Wu MB, Wu GL. The treatment of rheumatoid arthritis in 126 cases of venom compound capsule. Journal of Snake, 1999, 11: 30
- Xu JM, Song ST, Yu I CZ, Yang Y, Cui M, Wang WU, Xiong YL, Paradiso A Randomized, Double-blind, Placebo-controlled, Parallel Multicenter Trial of Cobrotoxin-containing Compound Analgesic in the Treatment of Postoperative Pain. Europain 2002; 2: Issue 2, Abstract
- Xu JM, Song ST, Feng FY, Huang FL, Yang Y, Xie GR, Xu LG, Paradiso A. Cobrotoxin-containing analgesic compound to treat chronic moderate to severe cancer pain: Results from a randomized, double-blind, cross-over study and from an open-label study, Oncol. Rep. 2006; 16: 1077-1084
- Zhu CZ, Li H, Yang QP, et al. The clinical treatment of diabetic kidney capsule of Cobra venom. Medicine and Pharmacy of Yunnan, 1997. 18: 460-461