

Cobroxin

for chronic pain

Cobra venom

DESCRIPTION

COBROXIN preparations are made from the venom of Asian cobras *Naja tripudians*. They are homeopathic formulations for oral administration and topical application.

Active ingredient: Cobra venom. See container for specific potency

PHARMACOLOGIC CATEGORY

Homeopathic.

INDICATIONS

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

Clinical experience shows that COBROXIN may also provide relief from other forms of pain; Cystitis, Cancer pain, Phantom pains, Rheumatoid arthritis, Osteoarthritis, Migraines, Trigeminal neuralgia, Sciatica and other neuralgias

PHARMACOLOGY

Elapids venoms were selected by homeopaths for their applications based upon their neurotoxic activity. It is therefore believed that the principal active components in the venoms are neurotoxins. These neurotoxins primarily target the cholinergic system by blocking the activity of acetylcholine (anticholinergics). Through this mechanism cobra venoms and cobra neurotoxins have recently been shown to have anti-inflammatory and analgesic activity. Cobra venom components have analgesic effects comparable to morphine but they are not addictive. **In order to achieve relief equivalent to that of morphine it should be noted that comparatively low doses of cobra venom are required.**

CONTRAINDICATIONS

- Nicotine
- Steroids
- Known allergy to venoms

PRECAUTIONS

- Can have additive effects with opiates.
- May lower blood pressure.
- Pregnancy: While there is no evidence contraindicating its use, there is always concern using any drug during pregnancy. Therefore, exercise caution before using COBROXIN.
- Nursing mothers: It is not known whether this drug is distributed into breast milk. As oral COBROXIN at the available strengths is non-toxic this is not a safety concern.
- Pediatric use: There is no clinical information on the use of COBROXIN in children and young adults. Consult a physician prior to use in these age groups.

INTERACTIONS

Cobra venom peptides can exert immunosuppressive effects. Exercise caution when administering similar drugs.

Cobra venom had additive effects when administered to animals using opiate analgesics. No contraindications with aspirin have been observed in animal studies.

ADVERSE REACTIONS

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

- In clinical studies where subjects were injected with cobra venom the following dose related adverse effects were reported; headache, nausea, vomiting, dry mouth, dizziness, sweating, palpitations, diplopia, nystagmus, hemiplegia.
- In clinical investigation with cobra venom administered orally the usual side effects were headache, nausea, vomiting, sore throat, allergic rhinitis and coughing

SERIOUS ADVERSE REACTIONS

Allergic reactions, sometimes severe (anaphylactic), to cobra venom have been reported when injected. Anaphylaxis is manifest usually within 30 minutes of administration. The use of antihistamines was found to alleviate the allergic reaction. Anaphylaxis is an **unlikely** occurrence with COBROXIN.

FORMATS

COBROXIN is supplied in two formats for Over-the-Counter use; oral and topical. Directions for use are provided on the box, which should be retained for reference.

DOSAGE AND ADMINISTRATION

Clarke in his book, *The Prescriber, A Dictionary of the New Therapeutics*, recommends the use of potencies ranging from 3X to 30X, with a dosing frequency of hourly to daily. Potencies supplied by the Company range from 4X to 5X. It has also been noted that the action may be more prompt if injected rather than given by mouth. Consult this text or Clarke's *A Clinical Repertory to the Dictionary of Materia Medica*, for specific treatment regimes.

Oral formulations require frequent dosing at first (2 spray at 3-4 hour intervals) until relief is attained when the dose can be reduced.

Topical formulations can be employed on an "as-needed" basis. Apply directly to the treatment site.

LATENT ACTION

It is important to note that there is a latent period of effect before the benefits of COBROXIN manifest themselves. Only with higher doses (>5X) will the effects of COBROXIN be apparent within a 12-24 hour period. In some individuals more time will be required to elicit a response that could extend up to 10 days.

STORAGE

Topical and oral suspensions may be stored at ambient room temperature (10-30 °C / 50-90 °F) away from direct sunlight. If desired it can also be stored refrigerated (2-8°C).

STABILITY

Liquid attenuations of cobra venom are stable for approximately 24 months when stored as directed.

TOXICITY STUDIES

Empirical studies on the toxicity of cobra venom have been conducted in several species of animals are summarized in table 1 below. Calmette (1901) established by injection the toxic dose of cobra venom in several species of mammals. However, 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 (Taylor, 1873). This is consistent with the data generated by Receptopharm in mice.

Recordings of the changes in blood pressure and respiration of dogs following the intravenous injection of cobra venom were made at the University of Maryland Medical School. The material used contained 166 mouse units per cc (1.66mg/ml). A pronounced depressor response was observed. Respiratory failure appeared to be the cause of death. In subacute toxicity studies on rats the same investigator gave 2 mouse units (0.02mg) of cobra venom intraperitoneally each day for 21 days. No demonstrable effects on the blood elements or blood chemistry were produced. There were no histologic changes detected in the livers, kidneys brains, or pituitary glands (Hill and Firor, 1952).

The injection of 1mg/Kg and above were associated with lethal outcomes in most species. The horse was noted as being quite sensitive to cobra venom.

Table 1: Toxicity tests conducted with cobra venom in-vivo.

Species	Reference	Route	Dose mg/Kg	LD50 mg/Kg	NOEL mg/Kg	Observations	
Mouse	Receptopharm Inc	p.o.	50	ND	ND	No toxicity observed	
	Calmette, 1904	s.c.	0.075	ND	ND	minimum lethal dose in 24 hours	
	Tseng et al., 1968	i.v.	0.2	ND	ND	Toxic, Survived >30min	
		s.c.	1	ND	ND	PK, toxic	
	Norris, 2008	s.c.	0.2	0.2	ND		
	Bhargava et al., 1970	i.p.	1.7	ND	ND	Death in 50 min	
	Shashidharamurthy et al., 2002	i.p.	0.5-5.0	0.7-2.0	<0.5	geographical variations	
Rat	Calmette, 1904	s.c.	0.66	ND	ND	minimum lethal dose in 24 hours	
	Macht, 1936	NR	0.02-0.12	ND	>0.12	Psychological changes	
	Hill and Firor, 1952	i.p.	0.08	ND	>0.08	No toxicity, organs normal	
Guinea pig	Calmette, 1904	s.c.	0.4	ND	ND	minimum lethal dose in 24 hours	
	Macht, 1936	NR	0.1	ND	>0.1	Lowers temperature	
Rabbit	Calmette, 1904	s.c.	0.5	ND	ND	minimum lethal dose in 24 hours	
	Macht, 1936	i.v.	0.025	ND	>0.025	No change in kidney function	
	Tseng et al., 1968	i.v.	1	ND	ND	Death in 25 min	
Cat	Macht, 1936	i.v.	1.04	ND	ND	Lethal dose	
Dog	Taylor, 1873	p.o.	15	ND	ND	no toxicity observed	
	Calmette, 1904	s.c.	0.8	ND	ND	minimum lethal dose in 24 hours	
	Hill and Firor, 1952	i.v.	1.6	<1.6	ND	Toxic,	
	Vick et al., 1966 fractions	Cobra venom	i.v.	0.5 CM Fr 1	<0.5	ND	EEG activity cease
			i.v.	0.5 CM Fr 5-8	<0.5	ND	Respiratory paralysis 30-120min, no change in ECG or BP
		i.v.	0.5 CM Fr 12	<0.5	ND	Cardiovascular decline, BP drop, EEG & Respiration normal,	
Horse	Calmette, 1904	s.c.	0.05	ND	ND	minimum lethal dose in 24 hours	
Human	Estimated	s.c.	0.25	ND	0.007-0.015	>0.015mg/Kg diplopia/hemiplegia/vomiting	

SAFETY PHARMACOLOGY

Respiratory

Respiratory failure due to paralysis of the muscle involved in respiration may occur after elapid (cobra and krait) envenomation (Karalliedde et al., 1988). Respiratory paralysis is 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 (Bawaskar and Bawaskar, 2004). Ventilatory care is easy to institute and is life saving. Respiratory distress in mice is readily observable. An oral toxic dose for COBROXIN has not been established and acute toxicity studies in mice have indicated no suggestions of respiratory deficits.

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 (Karalliedde et al., 1988). Vick et al (1966) fractionated cobra venom by cation exchange

chromatography and assayed the effects of the fractioned peaks in dogs by EEG, ECG and respiratory effects. 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 (Vick et al., 1966). There are pharmacologically distinct nicotinic acetylcholine receptors (AChR) are responsible for the differential effects of nicotine on heart rate however cobra neurotoxins are not ligands for these receptors. Furthermore studies have conducted whereby the toxic loop of Cobratoxin have been incorporated into the scaffold of Carybdotoxin, a potassium channel antagonist, with homology to the unique hERG potassium channel neurotoxins. HERG channels have been implicated in QT prolongation by certain pharmaceuticals though no biologic drugs have been described to induce this activity (Korolkova et al., 2001). This chimera had no activity on potassium channels yet retained the specificity for the NAChR (Drakopoulou et al., 1996). Consequently cobra neurotoxins do not have the ability to interact with hERG channels.

Central Nervous System

Numerous studies with alpha-neurotoxins in the CNS of developing chick embryos have demonstrated that Cobra toxin can provide beneficial effects when applied directly to the CNS or administered to embryos. It was also interesting to note Cobra toxin was not toxic to the developing chicks, a relevant teratogenic model. Embryos immobilized with neuromuscular blocking agents for differing periods between 4.5 and 9 days of incubation had an increased number of motoneurons in the brachial and lumbar lateral motor columns. Treatment with Cobra toxin on days 4--9, for instance, was able to prevent virtually all natural cell death during this period; control embryos had an average of 22,500 lumbar motoneurons on day 5.5, and 13,500 on day 10, whereas treated embryos had approximately 21,000 cells on day 10 (Pittman et al., 1979). Curare, Cobratoxin, Bungarotoxin and botulinum toxin were all about equally effective in preventing cell death. Treatment of embryos with nicotine or decamethonium (E6-E10) also reduced neuromuscular activity but did not alter motoneuron survival nor did such treatment alter AChRs (Oppenheim et al., 1989). 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 $\alpha 1$ -type nicotinic acetylcholine receptor binding activity was required for neuronal protection (Oppenheim et al., 2000), a pharmacological action clearly demonstrated for Cobra toxins. However, there is no clear evidence in animals that Cobra toxins can gain access to the CNS without direct administration (Tseng et al., 1968) unless the area is compromised such as in an inflammatory environment.

Reproduction and Teratogenicity

Controlled reproduction studies with cobra venom have not been conducted. No adverse effects were reported when treating pregnant women with 5X strengths doses (Bryson, 1954)

CLINICAL EXPERIENCE

Historically homeopathic proving of cobra venom employed the oral route of administration ranging from 1X to 60X (Russell 1853, Bayes 1876). The preferred oral dose of cobra venom was 4X (Hughes, 1870). Some investigators felt the venom was more effective if administered by injection. Several human clinical studies have been conducted with cobra venom administered by injection in addition to several studies being conducted from the 1990s onwards with purified neurotoxins also administered by injection but also orally (Table 2).

Table 2: Clinical Pain reports with Cobra venom and cobra neurotoxins

Year	Reference	Venom	No. of subjects	Dose	Route	Frequency	Duration	Application
1933	Montelesser	Cobra	115	1ug	s.c.	daily	NR	Cancer/cancer pain
1933	Lavastine and Korossios	Cobra	NR	1ug	s.c.	daily/e.o.d/ weekly	NR	Cancer pain
1935	Gayle and Williams	Cobra						Parkinson's Disease
1936	Macht	Cobra	10	4 -10ug	s.c.	single	n/a	lab test normals
1936	Macht	Cobra	115	10 -20ug	s.c./i.m./ i.v.	daily/e.o.d/ weekly	NR	Cancer pain/neuralgia
1939	Rutherford	Cobra	17	10-30ug	i.m.	daily/e.o.d/ weekly	4 months	Cancer/cystitis
1940	Black	Cobra	17	50ug	s.c.	21 doses	30 days	Cancer pain
1940	Steinbrocker et al	Cobra	65	n/r	s.c	NR	NR	Arthralgias
1947	Tan and Ines-Tan	Cobra	5	NR	NR	NR	NR	Herpes zoster
1952	Hill & Firor	Cobra	30	0.1-1.2mg	s.c.	twice daily /e.o.d/ weekly	30 days	Cancer pain/migraine
1953	Taren	Cobra	NR	NR	NR	NR	NR	Pain
1954	Bryson	Cobra	466	10-30ug	s.c.	weekly/ quarterly	>1 year	arthritis
1954	Lumpkin, Warfield & Firor	Cobra	66	10-30ug	s.c.	weekly/ quarterly	4 months	arthritis
1954	Oaks and Quinn	Cobra	NR	NR	NR	NR	NR	Ocular therapy
1954	Jackman	Cobra	NR	NR	NR	NR	NR	neuroses
1957	Meiselas, Austin & Schlecker	Cobra	14	10-30ug	s.c.	weekly	up to 6 month	osteoarthritis
1960	Williams	Cobra	8	NR	s.c.	e.o.d/ weekly	6 weeks	trigeminal neuralgia
1968	Singh and Srivastava	Cobra	30	+0.05-0.25	s.c.	weekly/ monthly	12 months	Asthma
1978	Wenshaw Derm. Inst.	Cobrotoxin	30	35ug	i.m.	daily	NR	Leprosy neuropathy
1980	Pu	Cobrotoxin	96	70ug	i.m.	daily	10 days	Headache, sciatica, trigeminal neuralgia
1980	Zeng	Cobrotoxin	64	70ug	i.m.	daily	NR	sciatica, back pain, RA, others
1991	Li and Zhou	Cobrotoxin	90	NR	NR	NR	NR	Heroin addiction
1991	Song	Cobra/Viper venom	7	NR	p.o.	3 caps/t.i.d	5 years	lung adenocarcinoma
1993	Zhou et al.	Cobra	96	0.6-1.3mg	i.v.	3h infusion.	7-10 days	Aute cerebral infarction
1995	Cao et al.	Cobrotoxin/Nefopam		+70/15	i.m.	1-2 daily	NR	Headache, sciatica, trigeminal neuralgia, joint and cancer pain
1997	Zhu et al.	Cobra	10	NR	p.o.	3 caps daily	120 days	Diabetes complications
1998	Gao	Cobrotoxin	182	70 ug	i.m.	daily	20 days	sciatica
1999	Wang et al.,	Cobrotoxin	72	0.25ug /Kg	i.t.	daily	NR	post-operative pain
1999	Wu and Wu	Cobra	126	2 capsules	p.o.	daily	3 months	Rheumatoid arthritis
1999	Wei et al.	Cobra	80	0.1mg	s.c.	daily	10 weeks	Periarthritis
1999	Zhu & Liu	Cobrotoxin	92	70ug	s.c./i.m.	daily	5 days	Acute and chronic pain
1999	Xiong	Cobrotoxin	300	NR	NR	NR	NR	Morphine addiction
1999	Wu and Wu	Cobra	126	NR	p.o.	2 caps/t.i.d	120 days	RA
1999	Li et al.	Cobra	492	NR	topical	1-3times/day	30 days	infection healing
2000	Wei and Hueng	Cobra venom/methotrexate	25	0.1mg	i.m.	e.o.d	6 weeks	RA
2001	Xu et al	Cobrotoxin +	100	NR	p.o.	single	1 day	post-operative pain
2001	Wu and Zu	Cobra	122	NR	p.o.	3 caps/t.i.d	30 days	digestive system cancer
2002	Xu et al	Cobrotoxin +	230	NR	p.o.	daily	7 days	Moderate to severe cancer pain
2007	Wei et al.	Cobra	80	0.1mg	i.m.	daily	2 weeks	Scapulohumeral periarthritis
		TOTAL	3378					

NR; not reported, e.o.d; every other day.

Doses of up to 0.55mg/Kg have been administered orally to humans without serious adverse effects. Primary side effects have been associated with headache. It is believed gastrointestinal disturbances reported in “provings” may have resulted from bacterial contamination of the venoms.

In most cases, limited toxicity was observed in the studies with cobra venom presumably due to the low doses employed. Table 3 outlines the responses and side effects reported with the use of cobra venom from the studies referenced above. Toxic effects were dose related and not limiting. At doses of 600 MU or 6mg (0.085mg/Kg) side effects included nausea, vomiting, dry mouth, dizziness, sweating, headache, palpitations, diplopia, nystagmus, hemiplegia. Estimated maximum tolerated dose by injection (MTD) is 4mg (approximates to 2X).

Table 3: Summary of reported responses and side effects of treatment with cobra venom

Year	Reference	Venom	Response	Side effects
1936	Macht, PNAS	Cobra	>60%	Nausea
1936	Macht, PNAS	Cobra	>90%	none reported
1938	Hill & Firor	Cobra	nr	diplopia/hemiplegia/vomiting
1939	Rutherford	Cobra	88%	none reported, 10ug maintenance
1954	Bryson	Cobra	82%	none reported
1954	Lumpkin, Warfield & Firor	Cobra	87%	2 allergic
1957	Meiselas, Austin & Schlecker	Cobra	0%	none reported
1960	Williams	Cobra	100%	None reported
1978	Wenshaw Derm. Inst.	Cobrotoxin	90%	Leprosy neuropathy
1980	Pu	Cobrotoxin	81%	headache
1980	Pu	Cobrotoxin	100%	sciatica
1980	Pu	Cobrotoxin	81%	trigeminal neuralgia
1980	Zeng	Cobrotoxin	90%	sciatica
1980	Zeng	Cobrotoxin	60%	Low back pain
1980	Zeng	Cobrotoxin	70%	RA
1980	Zeng	Cobrotoxin	83%	others; migraine, amputation, epilepsy
1991	Zhu et al.	Cobra venom	70%	NR
1995	Cao et al.	Cobrotoxin/Nefopam	33%	Cancer pain
1995	Cao et al.	Cobrotoxin/Nefopam	100%	Trigeminal neuralgia
1995	Cao et al.	Cobrotoxin/Nefopam	100%	Sciatica
1995	Cao et al.	Cobrotoxin/Nefopam	100%	Low back pain
1996	Wei and Hueng	Cobra venom /methotrexate	92%	NR
1997	Zhou et al.	Cobra venom	98%	NR
1998	Gao	Cobrotoxin	89%	sciatica
1999	Wang et al.,	Cobrotoxin	relief 2x morphine	dry mouth, nausea, dizziness
1999	Zhu & Liu	Cobrotoxin	>82%	dry mouth, nausea, dizziness
1999	Song	Cobra venom	n/a	7 with greater than 3 years survival
1999	Wu and Wu	Cobra venom	98%	NR
2001	Xu et al.	Cobrotoxin +	>90%	nausea, dizziness, sweating, hypodynamia, palpitation
2001	Wu and Zu	Cobra venom	92%	NR
2002	Xu et al.	Cobrotoxin +	>83%	similar to tramadol
2007	Wei et al.	Cobra venom	95%	NR

Reasonably consistent responses were observed in conditions treated with cobra venom between the American and Chinese studies. In one study Cobrotoxin was not as effective against cancer pain as had been previously reported for whole cobra venom suggesting that an accumulative effect of other neurotoxin and venom components contributes to the maximal effect. For example Cobrotoxin, which also has strong analgesic effects, is not found in appreciable quantities in Chinese cobra venom (*Naja atra*) but is found in Indian and SE Asian venom (loosely called *Naja tripudians*), which were the primary sources of the venom used in early American studies. Wang’s (1999) report of Cobrotoxin’s stronger analgesic effect when compared to morphine is supported by recent studies.

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Updated; 21 Jul, 2009