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ORIGINAL PAPER

Effect of a biostimulatory homeopathic complex on venom production in captive rattlesnakes (*Crotalus durissus*)

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The purpose of this study was to evaluate the effect of two administration methods of a biostimulatory homeopathic complex (*Convert H*®) on the production of fresh and lyophilized venom of rattlesnakes (*Crotalus durissus*) under intensive captivity conditions. Sixty snakes were subjected to treatment following a randomized block design. The effects of sex and size were controlled for. Thirteen consecutive extractions were performed over 21 months. The first factor considered in the experiment was the origin of mice used as prey: a conventional colony (A1) or the Convert H colony (A2; mice receiving the homeopathic complex in water at 1%). The type of water given to snakes was the second factor: pure (B1) or amended with 5% of *Convert H*® (B2). The experiment was structured in a factorial 2 × 2 design combining mouse and water types (A1B1, A1B2, A2B1, and A2B2). No consistent treatment effects on fresh venom production (mL) were observed when the experimental groups were compared with controls (A1B1). However, production of lyophilized venom (mg) was significantly higher ($p < 0.05$) in A2B2 animals than in controls in eight of 13 extractions performed, and also in aggregate. The results revealed that production of lyophilized venom, measured over multiple extractions, can be increased by administering the homeopathic complex simultaneously to rattlesnakes and prey. *Homeopathy* (2016) **105**, 338–343.

Keywords: *Crotalus durissus*; *Convert H*®; Fresh venom; Lyophilized venom

Introduction

Maintenance and breeding of snakes in captivity are activities of medical and scientific interest, made more relevant by recent findings on the potential effects of venom components.[1–4] However, studies investigating the relationship between captivity conditions or snake ecology and venom production have been infrequent.[5,6]

In Brazil, rattlesnake (*Crotalus durissus*) venom has been produced since 1938. The species is one of the most investigated for the medical and pharmaceutical interest in its venom and also because the species is the second most frequent cause of ophidian accidents.[7] Crotoxin, crotamine, gyroxin, convulxin, and 'thrombin-like' or 'thrombin-type' compounds have been isolated from its venom.[8] Crotoxin has antitumoral and analgesic effects, while crotamine also exhibits analgesic activity, and 'thrombin-like' compounds can be used in the production of a surgical adhesive.[8,9]

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The amount of venom produced by a snake depends on several factors, among them species, productive capacity of the venomous glands, habitat, photoperiod, temperature, age, size, ontogenetic stage of the animal, health conditions, duration of fasting, period between extractions, care in handling, and stress level.[10–14]

Fuller knowledge of factors that affect homeostasis of these animals and the development of treatment protocols to promote this condition are necessary for ensuring the well-being of snakes in captivity and increase venom production. To this end, homeopathy can be employed as an alternative therapy. First developed by Hahnemann, homeopathy is a non-poisonous therapeutic technique that leaves no chemical residues in the products and is capable of healing and maintaining the health of all living organisms.[15] Globally widespread, homeopathy is currently used both in human and veterinary medical treatment.

Convert H® is a biostimulatory homeopathic complex for protection against stress, developed by Brazil-based Empresa de Nutrição Animal Real & Cia. Ltda. Composed with Natrum muriaticum 10^{-60}, Calcium carbonicum 10^{-30}, Silicea terra 10^{-400}, and Hypothalamus 10^{-30}, the complex was developed to act on the endocrine system of animals, particularly improving liver function by enhancing the filtering and detoxifying capability of this organ, with the purpose of regulating organic functions, increasing the assimilation of nutrients, restoring and maintaining organic balance, and reducing the susceptibility of animals to stress, thereby increasing productivity, fertility, and performance of animals, both by stimulating natural defenses and physiological functions and reducing the levels of stress caused by environmental and climatic factors, as well as handling.

The effectiveness of *Convert H*® on animal growth and reproductive efficiency has been demonstrated in different studies. Teixeira *et al.*[16] observed higher weight gains in mice treated with this product. Zorzatto and Teixeira[17] and Zorzatto *et al.*[18] found increases in the numbers of mouse cubs born and weaned. Investigating ovines under food stress conditions, Chabel[19] observed improved immunological responses in animals treated with *Convert H*®.

The purpose of the present study was to compare the effects of two routes of administration of *Convert H*® on the production of fresh and lyophilized venom by rattlesnakes (*C. durissus*) maintained under intensive captivity conditions.

Material and methods

This research project, approved by the Ethics Committee on Animal Use (opinion 112/2006) of the Universidade Federal de Mato Grosso do Sul (UFMS), complies with requirements of the Brazilian National Research Council.[20]

Origin of snakes

The rattlesnakes, originated from several regions of Mato Grosso do Sul state, had been found by local residents and forwarded to the Universidade Católica Dom Bosco (UCDB) Animal Facilities, where the experiment was conducted. The UCDB Animal Facilities are registered with the Brazilian Institute of Environment and Renewable Natural Resources (IBAMA; registration number 170 855).

Animals

The 60 snakes employed in the study (24 males, 36 females) had been in captivity for at least two years and were subjected to adaptation to a diet of live mice two months before the experiment took place. They were kept in a separate room of the animal facilities, housed in opaque polyethylene boxes (39 cm × 59 cm × 31 cm; Marfinite) with lids and lateral holes. The boxes received corrugated paperboard substrate and an aluminum container mounted on an iron base for water supply. In order to measure the average evaporation in the room, another box, devoid of animals, was assembled reproducing the microenvironment. All boxes were kept in a temperature-controlled environment at 30 ± 5°C and relative humidity of 40–45%. The animals were fed once a month and had access to water *ad libitum*.

The preys provided for feeding were mice from two colonies: (*a*) a conventional colony of male and female heterogenic Swiss mice (*Mus musculus*) of conventional health standard,[21] originating from the UFMS Central Animal Facilities or the UCDB Animal Facilities; (*b*) the Convert H colony, of mice selected from the conventional colony 17 generations earlier and treated since then with 5 mL of *Convert H*® in 500 mL of drinking water. (The Convert H colony continues to be treated with the product.)

Hygiene of the environment and feeding of animals

The boxes were cleaned and the water supplies (60 mL) replaced three times a week.

The snakes were fed monthly at predetermined dates, always on the seventh day after extraction, and weighed one day before fed. The mice were given according to type of treatment and nutritional needs (15% of snake body weight of the snake). The approximate ratio between mouse and snake body weights was 3.6%.[22]

Venom extraction

Venom was extracted every 48 days, totaling 13 extractions in the experimental period. After each extraction the snakes were allowed to rest for seven days and subsequently fed. A new extraction was performed 41 days after feeding.

For venom extraction, each snake was maintained for 10 min on a heating plate (30 ± 2°C) with the aid of a herpetological hook and subsequently transferred into a clear polyvinyl chloride (PVC) tube, from which it was slid out and held immobilized in the posterior skull region by the handler's forefinger and thumb. Body length was measured using a measuring tape. Snout-vent length (SVL) (±0.1 cm) was also evaluated. For venom extraction, a slight pressure was made to elicit mouth opening and exposure of fangs, immediately introduced into the membrane of a collector. After extraction, a #12 nasogastric probe was inserted down to the esophagus, and a volume of water,

pure or with the homeopathic complex at 15 mL/kg added,[23] was administered to ensure that all snakes ingested at least a minimum amount of the product *via* drinking water. Untreated snakes were handled in the same manner, but using water devoid of homeopathic complex.

After each extraction, the production of fresh venom by each animal was measured with the use of a micropipette (0.001 mL accuracy; Labmate) as the venom was transferred from the extraction beaker to a 2 mL Eppendorf tube wrapped in aluminum foil, identified with animal number, and immediately frozen and dehydrated in a Liotop L101 benchtop freeze-dryer (Liobras). The lyophilized venom was then weighed (±0.1 mg) on an AG 200 analytical scale (Gehaka).

Experimental design

A random block design was employed to assign the snakes to groups, each composed of 15 blocks of four animals of the same sex and similar lengths and weights. The treatments were structured in a factorial 2 × 2 scheme. The first factor considered in the composition of treatments was the origin of mice: conventional colony (A1) or Convert H Colony (A2), the latter of which received *Convert H*® at 1%. The second factor was type of water: pure (B1) or amended (3 mL of *Convert H*® in 57 mL of pure water; 5% concentration) (B2).

Statistical analysis

SAS software, version 9.0 (SAS Institute, Cary, IN, USA) was used for statistical treatment. The data were tested for normality, homogeneity of variances, and presence of outliers, before inferential tests with a significance level of 5% were performed. Data on the production of fresh (±0.001 mL) and lyophilized (±0.1 mg) venom, both per extraction and in total, were subjected to logarithmic transformation to homogenize variances, but the estimates presented in the Results section were obtained by reverse transformation of the values found in the analysis. The results are therefore expressed in the same units as the original values.

Data on the production of fresh and lyophilized venom were subjected to repeated measures analysis using the mixed models method (MIXED procedure of SAS software). Type of mice, type of water, interaction between these types, and blocks were taken as factors between individuals; order of extraction was the factor within individuals, in addition to other interactions. The analyses were conducted according to Wolfinger and Chang,[24] Littell *et al.*,[25] and Littell *et al.*[26]

The best structure of the covariance matrix was selected by graphical evaluation of matrix R (the matrix of variances and covariances between orders of extraction) and by studying several statistics provided by the MIXED procedure of SAS—namely, −2 Res Log Likelihood (RLL), Akaike's Information Criterion (AIC), and Schwarz's Bayesian Criterion (BIC)—according to instructions from Kincaid[27] and Littell *et al.*[26] The study of statistics resulting from Restricted Maximum Likelihood of the null model was also performed to test the suitability of the structure $R = \sigma^2 I$ (independent errors). In addition, the covariance matrix was tested for sphericity using Mauchly's test to verify if the split-plot analysis considering time, used in the generalized linear model (GLM) procedure, was better than that specified in the MIXED procedure. Five structures were evaluated: Symmetric Composite (SC), Type H (Huynh−Feldt, HF), Toeplitz (TOEP), First Order Autoregressive (AR(1)), and Unstructured (UN).

Data on the production of total fresh and lyophilized venom were subjected to analysis of variance for a factorial 2 × 2 scheme in randomized blocks using the GLM procedure of SAS.

The Dunnett−Hsu test was used to compare the averages of least squares of treatment, considering A1B1 as the control treatment (no influence of *Convert H*®).

Results

Venom production varied widely between animals subjected to the same treatment, as well as in the productions by the same animal across the orders of extraction. Variations were significantly higher for fresh venom (mL) than for lyophilized venom (mg). Similar results were obtained by Mirtschim *et al.*[6] and Costa *et al.*[4] Substantial data variability was the main reason for use of the logarithmic transformation.

Costa *et al.*[4] observed significant variability in mean production of dry venom in *Bothrops*, *Crotalus*, and *Lachesis* snakes kept in long captivity.

Overall, the present results showed that production of fresh venom by extraction and production of lyophilized venom by extraction were both best described by unstructured covariance. The tests also indicated that neither of these dependent variables can be appropriately described as cases of split-plots in time.

For both extraction-related dependent variables, the effects of interaction with order of extraction were significant, except for the interaction between mouse origin and order, indicating the need for interaction unfolding.

No differences were expected between treatments for the first extraction, because up to that point the animals had been handled in exactly the same manner. In the second extraction, which occurred 48 days later, no differences were found between treatments, either. Only from the third extraction onwards was a significant difference obtained for treatment A2B2 in the production of lyophilized venom (Tables 1 and 2).

In general, fresh venom production increased across extractions, with a slight plateau between the 7th and 10th orders of extraction. For lyophilized venom production across extractions, increases were not expressive up to the 13th extraction, except for treatment A2B2.

With regard to fresh venom production (mL), no consistent effect of treatments was observed relative to controls (A1B1) across extractions, although some extractions exhibited significant differences for some treatments.

Overall, the results showed a steady, highly significant increase in production of lyophilized venom between the

Table 1 Least-squares means of fresh venom production (mL) for different treatments and orders of extraction (values obtained by inverse transformation: e^x)

Order	*Treatment*[(1)]			
	A1B1	*A1B2*	*A2B1*	*A2B2*
1	0.073	0.081	0.068	0.050
2	0.143	0.206	0.180	0.159
3	0.236	0.246	0.256	0.242
4	0.254	0.245	0.197	0.349
5	0.248	0.244	0.265	**0.393***
6	0.420	0.386	**0.533***	0.439
7	0.436	0.389	0.409	0.473
8	0.345	0.346	0.366	0.422
9	0.414	0.386	0.420	0.454
10	0.292	**0.444***	**0.428***	0.393
11	0.496	**0.267***	0.443	0.409
12	0.455	0.370	0.520	0.434
13	0.605	**0.306***	0.590	0.582

[(1)]A1: conventional colony; A2: Convert H colony; B1: pure water; B2: water amended with *Convert H*®. Asterisks indicate that means differ significantly from mean values of treatment (A1B1) (Dunnett–Hsu test).

Table 2 Least-squares means of lyophilized venom production (mg) for different treatments and orders of extraction (values obtained by inverse transformation: e^x)

Order	*Treatment* [(1)]			
	A1B1	*A1B2*	*A2B1*	*A2B2*
1	38.3	43.8	33.9	28.6
2	68.9	75.3	59.8	71.1
3	67.9	68.4	90.3	**101.3***
4	78.2	72.6	64.4	**158.0***
5	81.8	99.6	79.7	**222.6***
6	109.3	127.8	**155.8***	**279.0***
7	125.1	111.0	106.4	**318.2**
8	93.8	**214.6***	116.4	118.9
9	262.2	**92.9***	**134.1***	171.8
10	106.1	105.4	118.0	**231.2***
11	119.6	**174.2***	**88.2***	**187.7***
12	138.7	145.1	128.4	**214.5***
13	146.2	136.1	187.3	162.8

[(1)]A1: conventional colony; A2: Convert H colony; B1: pure water; B2: water amended with *Convert H*®. Asterisks indicate that means differ significantly from mean values of treatment (A1B1) (Dunnett–Hsu test).

3rd and 7th extractions for treatment A2B2 (homeopathic complex administered *via* water and prey). This treatment yielded higher production of lyophilized venom (in mg) than in controls in 8 of 13 extractions.

With respect to total venom production (13 extractions), a significant difference was observed only between treatment A2B2 (homeopathic complex by two routes) and controls (A1B1) for total production of lyophilized venom (mg). No significant differences were found for total production of fresh venom ($p > 0.05$; Figure 1).

Discussion

Venom production, both fresh and lyophilized, was generally higher than that reported in other studies conducted with the genus *Crotalus*. Belluomini[28] reported mean amounts of 0.12 mL and 28.5 mg for venom production by *C. durissus terrificus* in a controlled environment. For the same species, Roodt *et al.*[29] reported dry venom values of 140.4 ± 21.0 mg (mean ± standard deviation). Values similar to those obtained in the present study were reported by Glenn *et al.*[13] for *Crotalus atrox*, using electrical stimulation for extraction (0.83 mL for fresh venom; 228 mg for lyophilized venom). Grisolía *et al.*[12] found mean values of 67.6 ± 31.6 mg to 109.3 ± 36.4 mg for lyophilized venom. For *C. durissus cascavella*, Costa *et al.*[4] found a mean dry venom production of 76.48 ± 20.74 mg.

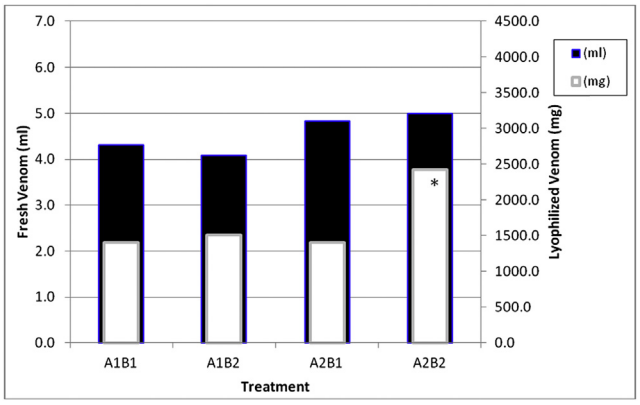

Figure 1 Least-squares means of total production of lyophilized and fresh venom across 13 extractions, with different treatments (values obtained by inverse transformation: e^x). A1: conventional colony; A2: Convert H colony; B1: pure water; B2: water amended with *Convert H*®. Asterisks indicate that means differ significantly from mean values of treatment (A1B1) (Dunnett–Hsu test).

According to Chippaux *et al.*,[30] effects such as seasonality affect venom amount and composition. However, the effects of seasonal changes or successive extractions have not drawn much interest from researchers. Williams and White[31] reported changes in venom production over a 12-month period, despite the absence of a consistent seasonal effect. Mirtschim *et al.*[6] found a regular and highly significant decrease in production during the colder months, although the absolute magnitude of this decrease was relatively inexpressive in comparison with factors such as body size. The absence of seasonal effect in the present study probably results from the controlled environment of the animal facilities. The gradual increase observed in venom production probably results from the stimulus caused by the extraction routine.

Well-designed experimental studies for the evaluation of treatments capable of promoting venom production are virtually nonexistent—a lack that precludes comparing the present results with those obtained elsewhere.

The expressively higher production of lyophilized venom observed in most extractions is probably a result of improved organic balance, which is the expected effect of the homeopathic complex. However, since the effect occurred only in the treatment involving homeopathic complex administration *via* two routes (water and prey), we suggest that the dosage received through one route may have been reinforced by the other, or that the effect of medication in water was enhanced by the effect generated by medication in the mice—*i.e.*, an association

between indirect and direct effects of medication is suggested. Mice from the Convert H colony exhibited more active behavior during feeding. Also, they exhibited stronger vitality and appeared more active overall, as well as more reactive to snakes. Lopes *et al.*[32] found that mice from the same colony were more active and aggressive than those not treated with homeopathy.

Teixeira *et al.*,[16] investigating mice chronically stressed by dietary restriction, observed that 6th-generation females from a colony treated with *Convert H*® had higher mean weight gain (-1.00 ± 2.33) than untreated animals (-6.00 ± 4.29). Also, weight gain was higher in treated females fed *ad libitum* (16.56 ± 5.63) than in untreated females (7.50 ± 3.13). Under normal feeding conditions, Zorzatto and Teixeira[17] found larger litter sizes at birth (10.01 ± 4.10) and weaning (9.15 ± 4.31) in the 7th, 8th, 9th, 10th, and 11th generations of mice treated with *Convert H*® than among untreated animals (8.49 ± 3.45 at birth and 7.87 ± 3.52 at weaning). In the same line of investigation, Zorzatto *et al.*[18] reported improved reproductive performance in mice treated with *Convert H*®, as shown by a higher proportion of parturitions in the 1st, 4th, 7th, 8th, 9th, and 10th generations (90.1%), in comparison with untreated animals (83.3%).

Considering the similarities between venom glands and salivary glands,[33] it is possible that visual and olfactory stimuli affected venom production. The higher vitality and activity of mice from the Convert H colony may have provided a visual stimulus that led to a higher production of venom. Glenn *et al.*[13] found that *C. atrox* produced more venom when fasted for longer periods before feeding with conventional mice than when fed a protein mixture administered *via* a probe. In this case, a higher production was observed for the type of handling that involved a higher level of stimulus during feeding. No published sources were found on the possible effects of a homeopathic product on different individuals along the food chain, but transmission of homeopathic information between food chain strata may constitute a hypothesis to explain these results.

Ultrastructural studies in venom glands of snakes of family Elapidae (*Maticora bivirgata* and *Lapemis curtus*) showed the presence of nerve endings next to the base of secretory cells.[34] Recent studies point out complex physiological mechanisms involved in the stimulation and inhibition of venom production by snakes. Of these, attention is drawn to the noradrenergic innervation, with involvement of adrenoceptors α and β, as well as calcium.[35,36]

Conclusions

The results revealed a significantly higher production of lyophilized venom when rattlesnakes received, simultaneously and across several extractions, the homeopathic complex *Convert H*® *via* water and prey.

Conflict of interest statement

The authors declare no conflicts of interest.

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