



Effects of *Tarantula cubensis* Extract on Electrocardiographic and Trace Element Status in Sheep

Remzi GONUL¹, Lora KOENHEMSİ^{1*}, Handan AYDIN², Tevfik GULYASAR³, Hasret DEMIRCAN YARDIBI⁴, Erman OR¹, Gulhan HOSTURK⁴, Abdulkadir UYSAL¹, Bora BARUTCU⁵

¹Istanbul University, Faculty of Veterinary Medicine, Department of Internal Medicine, Istanbul, Turkey

²Istanbul University, Faculty of Veterinary Medicine, Department of Pharmacology and Toxicology, Istanbul, Turkey

³Trakya University, Medical School, Department of Biophysic, Edirne, Turkey

⁴Istanbul University, Faculty of Veterinary Medicine, Department of Biochemistry, Istanbul, Turkey

⁵Istanbul University, Cerrahpasa Medical School, Department of Biophysic, Istanbul, Turkey

***Sorumlu Yazar /
Corresponding Author:**

Lora KOENHEMSİ
e-mail: lomkoh@istanbul.edu.tr

Geliş Tarihi / Received:
29 May 2014

Kabul Tarihi / Accepted:
18 August 2014

Anahtar Kelimeler:
Tarantula cubensis extract,
sheep, ECG, trace elements.

Key Words:
Tarantula cubensis ekstraktı,
koyun, EKG, iz elementler

Abstract

The purpose of this research was to investigate the acute effects of *Tarantula cubensis* extract (Theranekron, 1:100/D2, Richter Pharma, Austria) on some serum enzymes and trace elements, and the cardiovascular system in sheep. Seven sheep (age 6 months, 35±10 kg) were used in this study. Theranekron was applied in 6 ml doses subcutaneously. It was determined that in the serum Urea, Creatinin, ALT, ALP, G-GT, LDH, Ca and P levels were increased and T. protein, Mg, Cu, Fe, Zn and Se levels were decreased. The important results obtained after the treatment with Theranekron on cardiovascular system were blood pressure increases and some morphological changes in ECG. We concluded the Theranekron treatment can cause adverse effects in sheep and further investigation of the efficacy of Theranekron treatment is warranted.

Özet

Tarantula cubensis Ekstraktının Koyunlardaki Elektrokardiyografik Durum ve İz Elementler Üzerindeki Etkileri

Bu çalışmanın amacı *Tarantula cubensis* ekstraktının (Theranekron, 1:100/D2, Richter Pharma, Avusturya) koyunlardaki bazı serum enzimleri, iz elementler ve kardiyovasküler sistem üzerine olan etkilerini incelemektir. Bu çalışmada 7 koyun (6 aylık, 35±10 kg) kullanılmıştır. Theranekron 3 ml dozunda subcutan olarak uygulanmıştır. Serum üre, kreatinin, ALT, ALP, G-GT, LDH, Ca ve P seviyelerinin arttığı ve Total Protein, Mg, Cu, Fe, Zn ve Se seviyelerinin azaldığı belirlenmiştir. Threnekronla tedaviden sonra kardiyovasküler sistem üzerine görülen önemli sonuçlar kan basıncının artması ve EKG üzerindeki değişimlerdir. Theranekron tedavisinin koyunlarda yan etkileri olabileceğine ve Theranekronun etkinliği üzerine daha fazla çalışma yapılması gerektiğine karar verilmiştir.

Introduction

Homeopathy is a form of alternative medicine, which depends on the principle 'Like cures like = similia similibus curantur' first expounded by Dr. Samuel Hahnemann at the end of the 18th century (Gültiken and Vural, 2007; Kaçar et al., 2007). Emphasis in homeopathy remains the principle of 'like cures like',

and the belief that the body's own healing and regenerative capacity can be elicited to restore health (Pellitier, 2013). The first animal homeopathic treatment was started in 1785 by Baron von Boenninghausen (Kaçar et al., 2007). Von Boenninghausen treated different kinds of animals and introduced the principles of veterinary homeopathy

(Kaçar et al., 2007). It is imperative to use micro doses of homeopathic remedies. The effect of homeopathic medicines is strengthened upon successive dilutions. The aim for using homeopathic remedies is to restore health by stimulating the body to start healing (Kaçar et al., 2007).

For these reasons Theranekron which consists of *Tarantula cubensis* toxins, has found wide applications recently. It was used in cattle, horse, sheep, goat and dog (Sardari et al., 2007). Literature data confirmed that Theranekron can be successfully used in all necrotic, phlogenic and proliferative cases such as foot and nail decay, birth canal ulcer and abscess, foot and mouth disease, bluetongue, ectyema and sheep pox. It is emphasized that Theranekron stop tumor growth with demarcation in dogs with breast tumors and recurrence is not seen for years with a good quality of life (Albay et al., 2010; Lotfollahzadeh et al., 2012). Moreover, after difficulties in birth, it is used for lesions demarcation in the birth canal. It has been reported that cows in the postpartum period could prevent the formation of retentio secundinarium, reduce vaginal discharge and accelerate uterine involution after Theranekron application. Furthermore, Çam et al. (2007) used Theranekron in treatment of cutaneous papillomatosis in cows. Also this remedy is used in the treatment of abscess in burns, septicemia and toxemia. On the other hand, this kind of poisonous spider makes necrotic arachnidism and in some cases it can cause life threatening reactions like renal failure, disseminate intravascular coagulation (DIC), thrombocytopenia, coma, and convulsions (Boedler, 2002). Wang et al. (2008) reported that spider poison has a great deal of neurotoxin which destroys biological activity.

Tarantula cubensis extract (Theranekron, 1:100/D2, Richter Pharma, Austria) has many systemic effects such as antiphlogistic, demarcative, resolvent and regeneration (Çam et al., 2007; Gültiken and Vural, 2007; Kaçar et al., 2007; Sardari et al., 2007).

Nonetheless, there are not sufficient articles about the acute effects of Theranekron. Therefore the aim of this study is to investigate the acute effects of Theranekron in the cardiovascular system of sheep by analyzing ECG, blood pressure and oxygen saturation.

Materials and Methods

Seven Kivircik sheep which were 6 months old, 25-45 kg, not pregnant and healthy, taken from Istanbul University research farm were used in this study. Six ml subcutaneous injections of *Tarantula cubensis* extract

(Theranekron, 1:100/D2, Richter Pharma, Austria) were applied for the study. The changes in blood parameters, trace element levels, ECG, SpO₂ and blood pressure were recorded before and 2 hour after the injections.

Ten ml blood without anticoagulant was taken from v. jugularis of sheep. Biochemical blood parameters [ALT, ALP, GGT, urea, LDH, T.protein, Ca (Spinreact®), creatinin and P (Cormay®)] were determined spectrophotometrically (Tokio Boeki medical system TMS 1024). Trace element calculations were made with atomic absorption spectrophotometer (Shimadzu AA-6800). Se calculations were made with graphite oven (Shimadzu Graphite Furnace Atomizer GFA-EX7).

Electrocardiographic records were taken with the appropriate technique with Petaş Kardiyopet 300 machine. Blood pressure and oxygen saturation was measured with Edan M9B patient monitor. For this purpose, non-invasive blood pressure (diastolic, systolic and mean) was taken from femoral or metatarsal arteria depending on the animal's size. Oxygen saturation (SpO₂) was measured from arterial blood which is taken from the ear.

The mean values, standard deviations and statistical differences were performed by Student t-test. Value of P<0.05 was considered to be significant.

Results

Although the general status of the animals was normal in physical examination, after the Theranekron injection there was a skin reaction in one animal in the injection area which was resolved after 4 days (Figure 1).



Figure 1. Skin reaction after Theranekron® injection in a sheep.

Şekil 1. Bir koyundaki Theranekron® enjeksiyonu sonrasındaki deri reaksiyonları.

Two hours after the injection of Theranekron; serum creatinine, ALT, ALP, G-GT, LDH, Ca and P levels were increased and serum T. Protein, Mg, Cu, Fe, Zn and Se levels were found to decrease although there was no significant differences between the groups. Only Cu and Mg levels were significantly reduced ($P<0.05$) (Table 1).

SPO₂ and systolic and mean arterial blood pressure measurements were increased, diastolic blood pressure and oxygen saturation were decreased after the injection (Table 2). 2 hour after the injections one animal had a biphasic T wave, ST segment collapse and in another one there was an increase in Q and T amplitude (Figure 2) on the ECG recordings (Table 3).

Table 1. Changes in blood parameters in sheep 2 hours after the Theranekron® injection.

Tablo 1. Theranekron® enjeksiyonundan 2 saat sonra koyunlardaki kan parametrelerindeki değişimler.

	0 hour	2 hour
	X±Sx	X±Sx
Urea (mg/dl)	15.3±5.4	17.3±5.8
Creatinin (mg/dl)	0.8±0.3	1.1±0.2
ALT (IU/L)	35.6±36	48.6±54
ALP (IU/L)	209.9±170	716±605
G-GT (IU/L)	15±16	19±16
LDH (IU/L)	259±26	265±32
T. protein (g/dl)	8.6±2	8.2±1
Ca (mg/dl)	10±2.8	10.2±2.1
P (mg/dl)	5.4±0.8	5.6±0.8
Mg (mg/dl)	2.3±0.3	2.1±0.5*
Cu (µg/dl)	94.6±16	83.7±16.4*
Fe (µg/dl)	222.5±32.7	185.7±63.3
Zn (µg/dl)	43.6±13.5	34.8±17.6
Se (µg/dl)	136±29.9	109±21.5*

* $P<0.05$

Table 2. Changes in blood pressure and oxygen saturation in sheep 2 hours after the Theranekron® injection.

Tablo 2. Theranekron® enjeksiyonundan 2 saat sonra koyunlardaki kan basıncı ve oksijen saturasyonundaki değişimler.

	0 Hour	2 Hour
	X± Sx	X± Sx
Systolic (mmHg)	91.9±15	111.1±22.2
Mean (mmHg)	70±8.9	73.1±16.2
Diastolic (mmHg)	64.2±13.8	59±18.7
SpO ₂ (%)	95.7±6.4	93.2±6.3

Table 3. Changes in II. derivation of electrocardiography parameters in sheep 2 hours after the Theranekron® injection.

Tablo 3. Theranekron® enjeksiyonundan 2 saat sonra koyunlardaki elektrokardiyografinin II. derivasyonunda şekillenen değişimler.

	0 Hour	2 Hour
	X±Sx	X±Sx
P Amplitude (mV)	0.2±0	0.2±0
PR Interval (mm/sn)	0.09±0.02	0.1±0.04
QRS Interval (mm/sn)	0.06±0.02	0.05±0.01
R Amplitude (mV)	0.16±0.08	0.25±0.05
Q Amplitude (mV)	0.36±0.1	0.44±0.25
QT Interval (mV)	0.25±0.09	0.24±0.06
T Amplitude (mV)	0.2±0.1	0.2±0.1
T Wave (mm/sn)	0.03±0.01	0.04±0.01

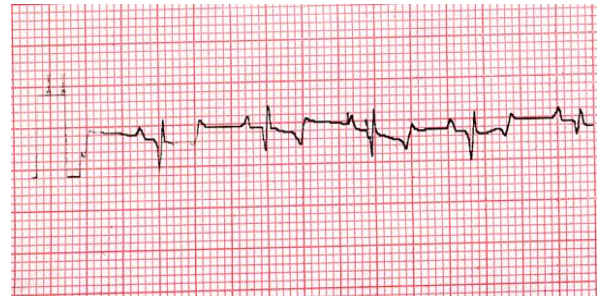


Figure 2. ST segment deviation and biphasic T wave on electrocardiography in a sheep in lead II after Theranekron® injection (50 mm/sec).

Şekil 2. Theranekron® enjeksiyonundan sonra bir koyunlardaki elektrokardiyografide II. derivasyondaki ST segmenti çökmesi ve bifazik T dalgası (50 mm/saniye).

Discussion

Theranekron is a homeopathic drug which is prepared from the Cuban tarantula, a dark-brown hairy spider, whose bite causes a gradually expanding scarlet areola and swelling around the bitten site (Lotfollahzadeh et al., 2012). There was a reddish skin reaction in one animal around the injection site in our study.

It was concluded that *Tarantula cubensis* stimulates the defence systems of the body. However the mechanism of *Tarantula cubensis* is still not clear

(Albay et al., 2010). Also there is lack of studies about the acute affects of this remedy. In our study, after Theranekron injection there is an increase in serum urea, creatinin, ALT, ALP, G-GT, LDH, Ca, P levels and a decrease in T. Protein, Mg, Cu, Fe, Zn, and Se levels. But no statistically significant difference were found in these paramaters only Cu and Mg levels were significantly reduced ($P<0.05$). Moreover, all values reported to be within reference values. Depending on the stress of animals, some changes can occur in behavior, physiology, hematology and neuro-hormone. Most of the trace elements related to enzymes, hormones and vitamins are known to serve as a part of them (Carlson, 1990; Dakka and Abdel-All, 1992; Fazio and Ferlazzo, 2003). Therefore, stress factors must be taken into consideration after injection of Theranekron and new studies should be done on this subject.

Researchers reported that (Cook, 2002; Fazio and Ferlazzo, 2003; Weisinger et al., 2004) the role of various hormones on stress heart rhythm and blood pressure increase, and plasma and catecholamine may cause changes in behavior. However, after Theranekron injection systolic and mean blood pressure increases, diastolic blood pressure and oxygen saturation decrease, these changes may be a result of the stress created by drug and its side effects.

Researchers reported that myocard is sensitive to oxygen insufficiency and it can be determined by ST segment deviation and T wave elevation in electrocardiography. ST segment changes characterized by elevation or depression of the ST segment according to the baseline (Başoğlu, 2002; Gertsch, 2009; Miller et al., 1999). Miller et al. (1999) reported that the increase in the amount of catecholamine in the circulation can cause changes in the T waves. In our research similar changes have been observed in electrocardiography, particularly after the injection, and this may cause myocardial hypoxia and myocardial ischemia. In the same way as oxygen saturation decrease may trigger myocardial hypoxia not in a significant level, medication side effects on the cardiovascular system is thought to be the cause. Wang et al. (2008) reported that although natural toxins are very useful for the preparation of different kinds of drugs, they have limited use because their affinity to the sodium channels and their strong cardiotoxic activity. The drugs effects we observed in our study might have resulted from their cardiotoxic effect.

Although Theranekron usage has started to increase, it can cause important clinical, biochemical and cardiovascular effects. We conclude that further

investigations must be performed about the side effects of the drug.

Acknowledgement

The authors wish to acknowledge Research Fund of Istanbul University for supporting this research (Project number: 3392).

REFERENCES

- Albay, M.K., Şahinduran, Ş., Kale, M., Karakurum, M.Ç., Sezer, K., 2010.** Influence of *Tarantula cubensis* extract on the treatment of the oral lesions in cattle with bluetongue disease. Kafkas Üniversitesi Veteriner Fakültesi Dergisi 16 (4), 593-596.
- Başoğlu, A., 2002.** P-QRS-T'nin morfolojik bozuklukları. In: Veteriner Kardiyoloji. Edit. Başoğlu, A. Çağrı Basın Yayın, Ankara. pp. 90-107.
- Boedler, C.R., 2002.** The brown spider *Loxosceles laeta*: source of the remedy *Tarantula cubensis*? Homeopathy 91, 166-170.
- Çam, Y., Kibar, M., Atasever, A., Atalay, Ö., Beyaz, L., 2007.** Efficacy of levamisole and *Tarantula cubensis* venom for the treatment of bovine cutaneous papillomatosis. Veterinary Record 160, 486-488.
- Carlson, G.P., 1990.** Clinical Chemistry Tests. In: Large Animal Internal Medicine. Edit by Smith, B.P. Third ed., Part IV, Mosby Company, USA, pp. 389-412.
- Cook, C.J., 2002.** Glucocorticoid feedback increases the sensitivity of the limbic system to stress. Physiology and Behavior 75, 455-464.
- Dakka, A.A., Abdel-All, T.H.S., 1992.** Studies on minerals picture in the blood sera of egyptian Sheep. Assiut Veterinary Medicine Journal 28, 242-249.
- Fazio, E., Ferlazzo, A., 2003.** Evaluation of stress during transport. Veterinary Research Communications 27, 519-524.
- Gertsch, M., 2009.** Electrolyte imbalance and disturbances, In: The ECG Manual: An Evidence-Based Approach. Springer, pp. 177-190.
- Gültiken, N., Vural, M.R., 2007.** The effect of *Tarantula cubensis* extract applied in pre and postoperative period of canine mammary tumours. Journal of Investigative Surgery 2, 13-23.
- Kaçar, C., Zonturlu, A.K., Oral, H., Yıldız, S., Arı, U.Ç., 2007.** İneklerde erken puerperal dönemde Theranekron uygulamalarının uterus involusyonu ve vaginal akıntı üzerine etkisi. Kafkas Üniversitesi Veteriner Fakültesi Dergisi 13, 11-15.
- Lotfollahzadeh, S., Alizadeh, M.R., Mohri, M., Dezfouli, M.R.M., 2012.** The therapeutic effect of *Tarantula cubensis* extract (Theranekron) in foot and mouth disease in cattle: a randomized trial in an endemic setting. Homeopathy 101, 159-164.

- Miller, M.S., Tilley, L., Smith, F., Fox, P., 1999.** Electrocardiography in Textbook of Canine and Feline Cardiology. Edit. Fox, P., Sisson, D., Moise, S. Saunders Comp., USA pp. 67-106.
- Pelletier, K.R., 2013.** Homeopathy: like cures like http://www.drpelletier.com/TBAM/excerpts/084-Homeopathy_Like.html (Accessed 24.04.2014)
- Sardari, K., Kakhki, E.G., Mohri, M., 2007.** Evaluation of wound contraction and epithelialization after subcutaneous administration of Theranekron® in cows. *Comparative Clinical Pathology* 16, 197-200.
- Wang, M., Liu, Q., Luo, H., Li, J., Tang, J., Xiao, Y., Liang, S., 2008.** Jingzhaotoxin-II, a novel tarantula toxin preferentially targets rat cardiac sodium channel. *Biochemical pharmacology* 76, 1716-1727.
- Weisinger, R.S., Blair-West, J.R., Burs, P., Denton, D.A., Purcell, B., Vale, W., Rivier, J., Weisinger, H.S., May, C.N., 2004.** Cardiovascular effects of long-term central and peripheral administration of urocortin, corticotropin-releasing factor, and adrenocorticotropin in sheep. *Endocrinology* 145, 5598-5604.