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Original Article
Özgün Araştırma

The effect of Theranekron® in intact and ischemia-reperfusion injured rat ovary

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Abstract: The effect of Theranekron® on ovaries were evaluated in healthy and ischemia- reperfusion injury rat model. Thirty-eight female, nulligravida Wistar Albino rats were divided into four groups, as follows: group 1: control, group 2: Theranekron®, group 3: ischemia-reperfusion and group 4: ischemia-reperfusion+Theranekron®. Each groups were analyzed biochemically and histologically. As compared with group 1, there was a significant increase in the number of atretic follicles and interstitial cells in group 2. Also, nitrite, nitrate, and malondialdehyde levels increased significantly in group 2. Group 3 represented intense hyperemia and hemorrhages on follicles surrounding the cortex and in the corpus luteum and marked increase in the number of atretic follicles, compared to group 2. Nitrite and nitrate levels in group 3 were similar to those in group 2, but malondialdehyde levels were lower than those in group 2. Group 4 showed very slight decrease in interstitial cells compared with group 2 and group 3. In this group, malondialdehyde levels decreased compared to group 2 and increased compared to control and group 3. Based on the results obtained, we may speculate that Theranekron® may have some degenerative effects on intact ovaries, and may have ameliorating effects on ischemia reperfusion injury in ovaries.

Keywords: Ischemia-reperfusion, Malondialdehyde, Nitrate/Nitrite, Rat, Theranekron®

Theranekron®'un sağlıklı ve iskemi-reperfüzyon hasarı oluşturulan rat ovaryumunda etkisi

Özet: Sağlıklı ve iskemi-reperfüzyon hasarı oluşturulan rat modelinde Theranekron®'un ovaryumlar üzerindeki etkisi değerlendirildi. Otuz sekiz adet nulligravida dişi Wistar Albino rat 4 gruba ayrıldı; Grup 1: kontrol, grup 2: Theranekron®, grup 3: iskemi-reperfüzyon ve grup 4: iskemi-reperfüzyon+ Theranekron®. Her grup biyokimyasal ve histolojik olarak analiz edildi. Grup 1'e göre grup 2'de atretik folikül ve interstisyel hücre sayısında anlamlı artış vardı. Ayrıca nitrit, nitrat ve malondialdehit seviyeleri grup 2'de anlamlı artış gösterdi. Grup 3'te yoğun hiperemi ve kanamalar mevcuttu. Grup 2'ye göre korteksi çevreleyen ve korpus luteumdaki foliküllerde ve atretik folikül sayısında belirgin artış oldu. Grup 3'teki nitrit ve nitrat seviyeleri grup 2 ile benzer, ancak malondialdehit seviyeleri grup 2'den düşüktü. Grup 4, grup 2 ve grup 3 ile karşılaştırıldığında interstisyel hücrelerde çok hafif azalma gösterdi ve ayrıca daha az atretik folikül gözlendi. Bu grupta malondialdehit düzeyleri grup 2'ye göre azalmış, kontrol ve grup 3'e göre yükselmiştir. Elde edilen sonuçlara dayanarak, Theranekron®'un sağlam yumurtalıklar üzerinde bazı dejeneratif etkilere sahip olabileceğini ve yumurtalıklarda iskemi reperfüzyon hasarı üzerinde iyileştirici etkileri olabileceğini tahmin edebiliriz.

Anahtar kelimeler: İskemi-reperfüzyon, Malondialdehit, Nitrat/Nitrit, Sıçan, Theranekron®

Introduction

The ovary is a complex endocrine organ, which shows structural and functional changes during the reproductive cycle in humans and mammals (Şahinarslan 2009). Although torsion of the ovary is generally associated with pregnancy (Parashar and Uppal 2011), it may also occur in prepubertal and postmenopausal periods (Akalın 2014). Ovarian torsion is defined as rotation of certain parts or complete of the ovary around its vasculature axis (Parashar and Uppal 2011). In humans, ovarian torsion accounts for 2.7% of emergency gynecological cases. Delays in the diagnosis of ovarian torsion or misdiagnosis may cause the patient to lose the ovarium or follicular reserves (Kavak et al. 2014). Reperfusion therapy (surgical interventions and drugs) is required to

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restore tissue perfusion in cases of ovarian torsion (Birincioğlu 2004). Detorsion in cases of adnexal torsion may have systemic and local consequences due to reperfusion of the ovaries (Demirci et al. 2004).

Reactive oxygen species, malondialdehyde (MDA), and many other toxic metabolites are released into the blood and tissue during ovarian torsion (Ohkawa et al. 1979; Turkoz et al. 2004; Cadırcı et al. 2010). Malondialdehyde exerts toxic effects, binding to amino groups of proteins, nucleic acids, or phospholipids (Akalın 2014). Nitric oxide (NO) is a vasodilator agent derived from the vascular bed of highly reactive tissues of endothelial origin, with extremely fast- and short-acting effects. In ischemia, superoxide anions are generated and combine with NO. As a result, peroxynitrite, which is an extremely toxic metabolite, is produced, resulting in severe damage in cerebrovascular tissue (Demirci et al. 2004).

Theranekron® is a homeopathic medicine prepared from the poison of a dark brown hairy Cuban tarantula *Tarantula cubensis*. The poison emitted by the bite of this tarantula causes both spillage and necrotic lesions in the skin. The poison has been reported to cause death and to have systemic effects in children (Gürbulak et al. 2014). However, Theranekron® also has beneficial effects and is used for the treatment of burns, gangrene, septicemia, and toxemia (Richardson-Boedler 2002). In addition, Theranekron® is used in the treatment of genital microbial diseases, uterine involution, endometriosis and cutaneous papillomatous diseases (Kaçar et al. 2007; Dolapcioglu et al. 2013; Adib-Hashemi et al. 2016).

To our knowledge, there have been no studies of the effects of Theranekron® on healthy ovaries or ovarian torsion. The aim of the present study was to investigate the histological and biochemical effects of Theranekron® on ovaries of healthy adult rats and rats with ischemia-reperfusion injury.

Material And Methods

The study was performed in the Experimental Animal Laboratory, Faculty of Veterinary Medicine, Hatay Mustafa Kemal University. Thirty-eight female Wistar Albino rats (obtained from Hatay Mustafa Kemal University Experimental Animal Department, Hatay, Turkey) aged 8-10 wk were used in this study, with a mean body weight of 220±25 g. Rats were housed in standart polycarbonate cages under controlled humidity and room temperature with 12/12 h light/dark cycles. Fresh water and diet were supplied *ad libitum*.

The animals were anesthetized with 60 mg/kg of intramuscular ketamine hydrochloride (Ketan's, Eczacibaşi, Pharmaceutical, Turkey) and 7 mg/kg of xylazine hydrochloride (The Romper, Bayer Pharmaceutical, Germany) before the procedures (Lebovic et al. 2004). For preventing hypothermia, during operations, we regulated the resting room temperature by using air conditioner. And all of the rats were decapitated after taking the blood samples. The study was approved by the Experimental Animals Ethics Committee of Mustafa Kemal University. All the experiments were performed in compliance with international guidelines on the ethical use of animals. The rats were divided into four groups, as follows:

Group 1 (control): This group consisted of healthy adult rats whose ovaries were removed after anesthesia without being subjected to any treatment (n = 8).

Group 2 (healthy group with Theranekron® treatment): The rats were treated with a single dose of intraperitoneal (ip) 0.3 mg/kg of Theranekron® (Theranekron® 50 mg, Richter Pharma, Wels, Austria) (Dolapcioglu et al. 2013) and the ovaries were removed 3 h later under ketamine-xylazine anesthesia (n =10).

Group 3 (ischemia-reperfusion): For ischemia, the adnexa were torsioned 360^0 after incision of the left fossa paralumbalis area, and then fixed on abdominal wall to stay for 3 h by using a Clip Turcica apparatus, (Fig. 1) which is a malleable, aluminum device that facilitates holding and release of the adnexa during a period of experimental ovarian ischemia and reperfusion (Hascalik et al. 2005). Incision was sutured; then, re-laparotomy was performed and adnexa were detorsioned; reperfusion was allowed for additional 3 h. After reperfusion, ovaries were removed (n = 10) (Hascalik et al. 2005; Ergun et al. 2010).

Group 4 (ischemia-reperfusion injury and Theranekron® treatment): For ischemia, the adnexa were torsioned 360^0 after incision of the left fossa paralumbalis area, and then fixed on abdominal wall to stay for 3 h by using Clip Turcica. Incision was sutured; a single dose of 0.3 mg/kg of Theranekron® was administered intraperitoneally (Ergun et al. 2010). Then, re-laparotomy was performed and adnexa were detorsioned; reperfusion was allowed for additional 3 h. After reperfusion, ovaries were re-

moved (*n* = 10) (Hascalik et al. 2005; Ergun et al. 2010).

For the histological examination, tissue samples were fixed rapidly with 10% neutral formaldehyde for light microscopic examinations. Tissue samples were then dehydrated and fixed with a graded alcohol series from 70% to 100% and xylene series after 24 h of washing in tap water. After being kept in xylene, samples were embedded in paraplast and transversal sections were taken. Crossman's modified triple staining technique (Denk et al. 1989) was applied to the 4-5 µm serial sections taken from the prepared paraffin blocks to reveal the general structure of the tissues (Denk et al. 1989) and examined under a CX21 Olympus binocular light microscope (Olympus corporation, Japan). Photographing of tissue sections were performed with an Olympus BX50 research microscope. The criteria for ovarian injury were tissue damage, degeneration of germinal epithelium and ovarian follicles, hyperemia and haemorrhage.

For the biochemical analysis, blood samples were taken from the heart and transferred to EDTA tubes. The tubes were centrifuged at 2000 rpm for 10 min at 4°C to separate the plasma, and the plasma was stored at -20°C. A colorimetric kit (Cayman Chemical/780001, USA) was used to determine plasma nitrate and nitrite levels.

Plasma MDA levels were determined by spectrophotometrically according to the method of Ohkawa et al. (1979). For this purpose, plasma samples were incubated at pH 3.5 for 1 h in a boiling water bath. A pink color indicated end products of MDA and thiobarbituric acid. Spectrophotometric measurement at 532 nm of the pink color complex is directly proportional to MDA levels.

Statistical analysis

All the biochemical values were expressed as mean±standard error. The results of groups were analyzed by ANOVA with posthoc Duncan test (SPSS for Windows, release 23.0). $p<0.05$ difference was considered significant.

Results

In ovarian sections obtained from the group 1 (control group), various organ-specific histological structures, including germinal epithelium, follicles, and corpus luteum were observed. In the medulla region, vascular structures were observed in the histological analysis (Fig. 2).

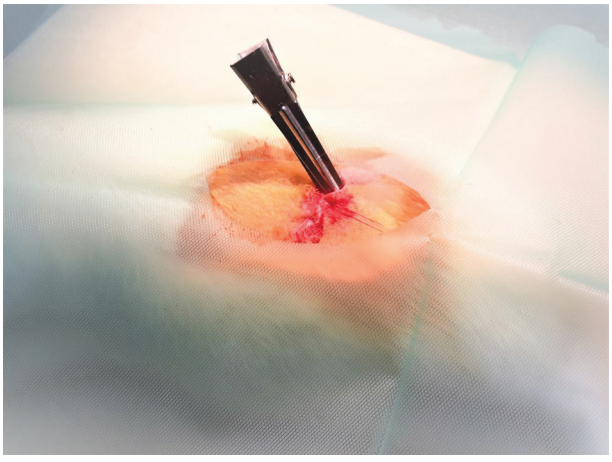

Figure 1: Ischemia-reperfusion via Clip Turcica apparatus

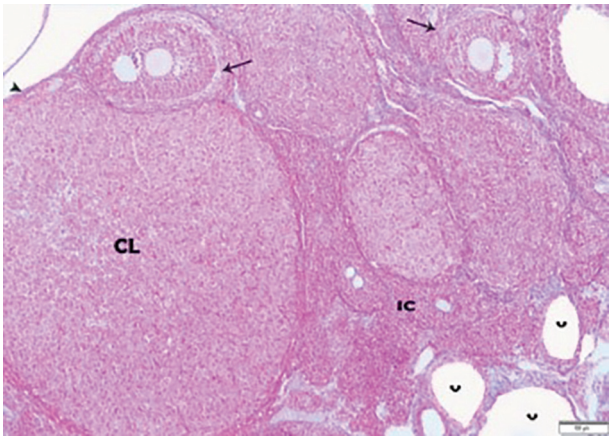

Figure 2: Group 1 (Control group); The histological section of rat ovaries. CL: Corpus Luteum, v: vessel, IC: interstitial cells, arrow: secondary follicles, arraow head: Germinal epithelium. Tripple staining method. Bar: 100 µm.

Compared with the control group, group 2 (Theranekron® treatment) showed no tissue damage or degeneration of the germinal epithelium surrounding the ovaries. Slight degeneration was seen in the follicles. Moreover, there was a marked increase in the number of atretic follicles. In the veins of the medulla region, hyperemia was observed and there was a significant increase in connective tissue cells in interstitial areas (Fig. 3). In the cortex area, focal bleeding (hemorrhage) areas were detected in the corpus luteum. In addition, hyperemia was observed in corpus luteum veins (Fig. 4).

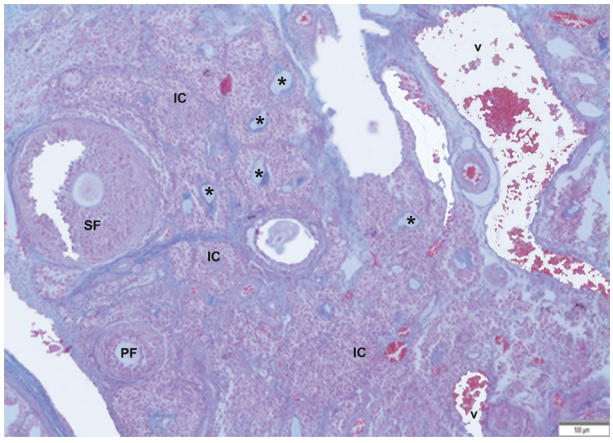

Figure 3: Group 2 (Theranekron group); The histological section of rat ovaries. PF: Primer Follicle, SF: Seconder Follicle, *: atretic follicle, IC: interstitial cells, v: vascular hemorrhage. Tripple staining method. Bar: 100 µm.

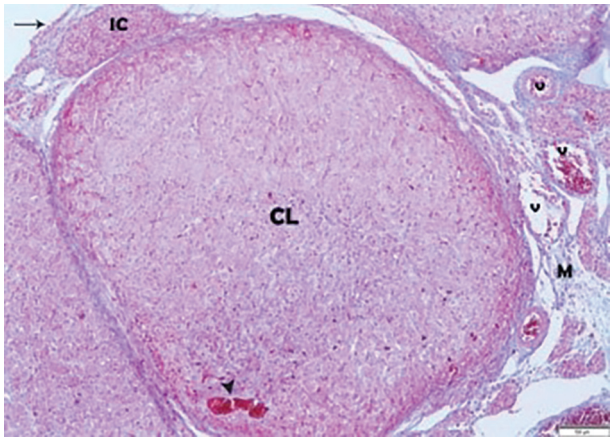

Figure 4: Group 2 (Theranekron group); The histological section of rat ovaries. CL: Corpus Luteum, IC: interstitiel cells, M: Medulla, v: vascular hemorrhage, arrow head: hemorrhage, arrow: Tunika albuginea, Tripple staining method. Bar: 100 µm.

In group 3, in general, there was no change in tissue integrity as compared with that observed in the control group. Histological appearance of medulla region was similar with group 2, whereas areas of interstitial cells presented more intense hyperemia and hemorrhages compared to group 2 (Fig 5). In addition, amount of connective tissue in interstitial regions were similar with group 2. Also, intense hyperemia and hemorrhages were also observed on follicles surrounding the cortex and in the corpus luteum and there was a marked increase in the number of atretic follicles compared to group 2 (Fig. 6).

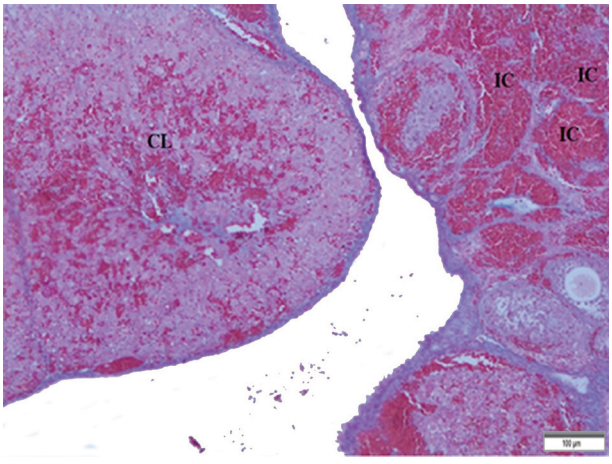

Figure 5: Group 3 (İschemia- reperfusion group); The histological section of rat ovaries. CL: corpus luteum; hemorrhage and hyperemia, IC: interstitial cells hemorrhage. Tripple staining method. Bar: 100 µm.

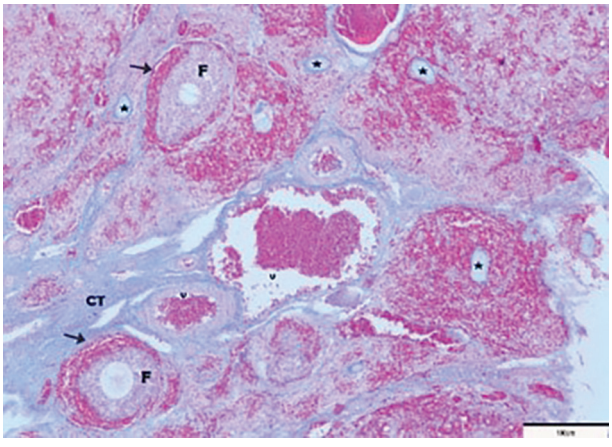

Figure 6: Group 3 (İschemia- reperfusion group); The histological section of rat ovaries. F: follicles, CT: connective tissue, v: vascular hemorrhage, arrow: theca follicle hemorrhage, *: atretic follicle. Tripple staining method. Bar: 100 µm.

Tissue integrity was similar in group 4 compared with other groups. However, fewer atretic follicles was observed in group 4 compared with group 2 and group 3. Hyperemia and hemorrhages were reduced in cortex and medulla region very slightly, compared to group 3. Also, group 4 showed very slight decrease in interstitial cells compared with group 2 and group 3 (Fig. 7, 8).

The nitrite/nitrate and MDA levels of the groups are presented in Table 1. As compared with those in the control group, nitrite and nitrate levels in group 2 increased significantly ($p < 0.05$) due to a significant increase ($p < 0.05$) in nitrite levels. MDA levels, which provide information about tissue and

cell damage, also increased significantly as compared with those in the control group ($p < 0.001$). These results were consistent with the histological findings.

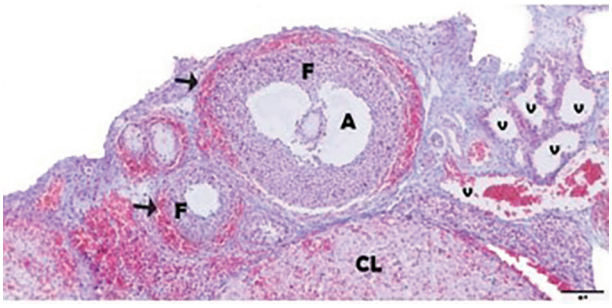

Figure 7: Group 4 (ischemia-repurfusion+Theranekron® group); The histological section of rat ovaries. F: follicles, CL: corpus luteum, A: antral follicle, v: vessel and vascular hemorrhage, arrow: theca follicle hemorrhage. Tripple staining method. Bar: 100 µm.

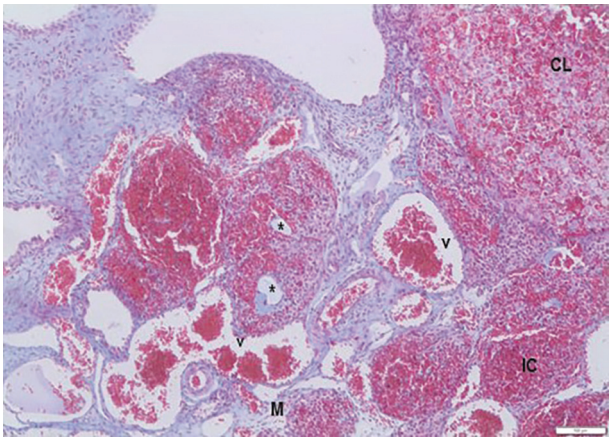

Figure 8: Group 4 (ischemia-reperfusion+Theranekron® group); The histological section of rat ovaries. M: Medullar region, IC: intersititial cell, CL: corpus luteum, hemorrhage and hyperemia v: vascular hemorrhage *: atretic follicle. Triple staining method. Bar: 100 µm

Table 1. Plasma Nitrite, Nitrate and MDA levels of the experimental groups (Mean ± SE)

Groups	Nitrate + Nitrite µM	Nitrite µM	Nitrate µM	Nitrite/Nitrate	MDA µM
Control (Group 1) (n=8)	48,01±4,47 [a]	10,73±3,26 [a]	37,28±5,24	0,37±0,13	3,35±0,21 [a]
Theranekron (Group 2) (n=10)	73,22±6,81 [b]	35,71±4,93 [b]	37,50±3,68	1,20± 0,24	5,53±0,35 [b]
Ischemia- reperfusion (Group 3) (n=10)	77,79±7,30 [b]	30,40±6,75 [b]	47,40±8,70	1,87±1,27	3,79±0,34 [a]
Ischemia-reperfusion+Theranekron (Group 4) (n=10)	65,67±3,69 [ab]	30,79±5,37 [b]	34,87±4,85	1,02±0,22	5,00±0,36 [b]
	p<0,05	p<0,05	-	-	p<0,001

a,b,: The difference between values with different letters in the same column is significant (p<0,05; p<0,001).

In Group 3, nitrite levels ($p < 0.05$), nitrite and nitrate levels ($p > 0.05$), and the nitrite:nitrate ratio ($p > 0.05$) increased as compared with those in the control group, with the findings similar to those observed in group 2. In group 3, MDA levels were lower ($p < 0.001$) as compared with those in group 2 but showed no significant change as compared with those in the control group.

Compared with the control group, both nitrite and MDA levels increased in group 4 ($p < 0.001$). As compared with group 3, although not statistically significant, the nitrate level and nitrite:nitrate ratio were decreased, and MDA levels were elevated ($p < 0.001$). Levels of nitrate and nitrite, levels of MDA and the nitrite:nitrate ratio were decreased in Group 4 as compared with those in Group 2 ($p > 0.05$).

Discussion and Conclusion

Most studies of Theranekron® have involved livestock due to its uses in veterinary medicine (Lotfollahzadeh et al. 2012; Gürbulak et al. 2014; Gönül et al. 2015) Theranekron® has been used as a homeopathic remedy in the treatment for lesions in the endometrium and lesions in the mouth, feet, and nails (Stampa 1986; Oryan et al. 2012; Dolapcioglu et al. 2013; Adib-Hashemi et al. 2016) However, according to a literature survey, there have been no studies of the effects of Theranekron® on healthy tissues.

In the present study, Theranekron® administration to healthy rats significantly increased plasma nitrite and MDA levels. The results of the histological analyses revealed an increased number of atretic follicles, hyperemia in veins of the medulla region, focal bleeding areas (hemorrhage) in the cortex

area of the corpus luteum, and hyperemia in corpus luteum veins, in addition to a significant increase in connective tissue cells in interstitial areas. In the present study, since Theranekron® increased the number of atretic follicles in the healthy rat ovary, it can reduce the follicle reserve and suppress normal follicle development (Hirshfield 1989). Reports of adverse effects in homeopathic publications were not well documented and also case reports in medical journals usually pointed more to adverse effects of mislabelled 'homeopathic products' than to true homeopathic medicines (Dantas et al. 2000). By this study, it can be reported that Theranekron®, as a homeopathic remedy, have some adverse effects on healthy rat ovaries. On the other hand, during the ischemia-reperfusion injury, regarding to the decreased amount of atretic follicle, Theranekron® treatment may not show this adverse effect.

In this study, in Group 3, ischemia-reperfusion was induced in the ovaries of the rats by torsion and detorsion using a Clip Turcica apparatus, and the ovaries were then examined. A previous study showed that ovarian torsion in reperfused ovaries caused venous congestion, hemorrhages, and necrosis in tissue due to deterioration in interstitial cells and follicular structures (Oelsner et al. 1993). Moreover, research reported extensive vascular congestion, hemorrhages, and edema (Bostancı et al. 2016). In the present study, in accordance with the findings of the aforementioned literature, we observed intense hyperemia and hemorrhages in the cortex and structures of the corpus luteum. Previous studies reported that ovarian Lipid peroxidation (LPO) and/or MDA levels increased after ischemia-reperfusion in rat ovaries (Turkoz et al. 2004; Cadirci et al. 2010). In the present study, ischemia-reperfusion (Group 3) increased plasma MDA levels as compared with those of the control group, but the finding was not statistically significant. As shown by the histological findings in the present study, tissue damage was compatible with elevated tissue MDA levels reported by previous studies (Turkoz et al. 2004; Cadirci et al. 2010). However, the rise of ovarian tissue MDA levels (Turkoz et al. 2004; Cadirci et al. 2010) seemed not to reflect plasma MDA levels, as shown in our study. To the best of our knowledge, the effects of Theranekron® on tissue or plasma MDA levels were not reported. Further research is needed to elucidate the effects of Theranekron® on tissue damage regarding oxidative stress and lipid peroxidation.

According to a literature review, there have been no previous studies of the use of Theranekron® in cases of ischemia-reperfusion. Dolapcioglu et al. (2013) reported that Theranekron® gave rise to fibrous and vascular tissue around endometrial follicles of rats. In the present study, there was an increase in interstitial cells in both group 2 and group 3. However, in group 4 notable decrease of interstitial cells compared to group 2 was observed, on the other hand, compared to group 3, there was an unobvious decrease regarding the interstitial cells. Nitrite levels in group 4 (Theranekron® treatment after ischemia-reperfusion) showed an insignificant decrease as compared with those in group 3. This finding explains the slight decrease in hemorrhages observed histologically, in group 4. Plasma MDA levels increased significantly in group 4, as compared with those of group 1 (control) and group 3. This finding suggests that Theranekron® may result in an increase in MDA levels both in intact rats and rats exposed to ischemia-reperfusion. On the other hand, Theranekron® may reduce the degeneration in ischemia-reperfusion injury, since it decreased the amount of atretic follicules in group 4 compared to the group 2. As we determined plasma MDA levels in this study and plasma levels may not reflect the tissue MDA levels (Turgut et al. 2006; Abdel-Hafez et al. 2010) we may not detected the ovarian tissue MDA levels in group 4.

In this study, hemorrhages and hyperemia were detected histologically, depending on the administered dose and time of Theranekron®. Moreover, the biochemical analyses revealed that Theranekron® treatment was associated with an increase in blood plasma nitrite, nitrate, and MDA levels of both healthy and ischemia-reperfusion injury in rats. Based on the results, we may speculate that Theranekron® may have some degenerative effects on intact ovaries, and may have slight remedial effects on ischemia reperfusion injury in ovaries. As Theranekron® was also used in endometriosis and uterine involution successfully, we suggest that the effects of Theranekron® on healthy ovaries and ovaries exposed to ischemia-reperfusion injury can provide insight into utilization of Theranekron® treatments in disorders of reproductive system organs. In addition, further studies are needed to determine the optimum remedial dose of Theranekron® on ischemia reperfusion injury in rat ovaries.

Ethics committee for the use of experimental animals: The study was approved by the Experimental Animals Ethics Committee (Year 2013 - No: 12/4) of Hatay Mustafa Kemal University.

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