



## RESEARCH ARTICLE

### Cardiac safety of gamithromycin in ewes

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### Koyunlarda gamitromisin kardiyak güvenirliliđi

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#### Öz

**Amaç:** Bir makrolid antibiyotik olan gamitromisin sığırlarda pasteurellosis tedavisinde önerilmekle birlikte koyunlarda etiket dışı olarak kullanılmaktadır. Makrolid antibiyotiklerin kardiyotoksik etkileri bilinmektedir, ancak gamitromisin koyunlarda kardiyak güvenirliliđi ile ilgili bilgi bulunmamaktadır. Araştırmanın öncelikli amacı koyunlarda gamitromisin kardiyak güvenirliliđini belirlemektir. Bunun yanı sıra karaciđer ve böbrek fonksiyonlarına ve hemogram parametrelerine etkisini tespit etmektir.

**Gereç ve Yöntem:** Araştırmada 10 adet koyuna gamitromisin (6 mg/kg, SC) tek doz olarak uygulandı. Kan örnekleri uygulamadan önce (0. gün, kontrol) ve sonraki 0.25, 0.5, 1, 2, 3, 4, 5, 6, 7, 8 ve 9. günlerde alındı. Spesifik kalp hasar belirteçleri olan serum kreatin kinaz-MB kütle ve troponin I düzeyleri, karaciđer ile böbrek hasar belirteçleri ve hemogram parametreleri ölçüldü.

**Bulgular:** Araştırmada troponin I düzeyinde birinci gün istatistiksel olmayan yükselmeler belirlenirken, kreatin kinaz-MB kütle düzeyinde deđişimler belirlenmedi. Total bilirubin, total protein, kreatinin ve akyuvar düzeyinde referans deđerler arasında istatistiksel deđişimler belirlendi (P<0.05).

**Öneri:** Koyunlara tek doz gamitromisin (6 mg/kg, SC) uygulamasının kalp, karaciđer, böbrek fonksiyonları ile hemogram parametrelerine belirgin yan etkilerinin olmadığı ifade edilebilir.

**Anahtar kelimeler:** Koyun, gamitromisin, güvenirlilik

#### Abstract

**Aim:** Gamithromycin, a macrolide antibiotic, is used in the treatment of bovine pasteurellosis, whereas it is used in sheep as extra-label. It is well known that macrolide antibiotics have cardiotoxic effect, however, it cannot be found the information of cardiac safety of gamithromycin in sheep in the literature. The first aim of this research was to determine the cardiac safety of gamithromycin in sheep. In addition, effects of gamithromycin on the liver and kidney functions and hemogram values were investigated.

**Materials and Methods:** Gamithromycin (6 mg/kg, SC) was administered as a single dose to 10 sheep. Blood samples were taken before (0. day, control) and after treatments at 0.25, 0.5, 1, 2, 3, 4, 5, 6, 7, 8 and 9 days. Serum creatine kinase-MB mass and troponin I levels which are specific cardiac damage markers, liver, kidney damage markers and hemogram values were measured.

**Results:** Increased troponin I levels were determined at first day but it was not statistically significant, and there was no change determined in the creatine kinase-MB mass levels. Statistically significant (P<0.05) fluctuations were determined in the total bilirubin, total protein, creatinine and white blood cell counts, but these results were within the normal ranges.

**Conclusion:** It may be stated that single dose (6 mg/kg, SC) gamithromycin administration has no distinctive side effects on the heart, liver and kidney functions and hemogram values in sheep.

**Keywords:** Sheep, gamithromycin, safety





## Introduction

Semi-synthetic antibiotic gamithromycin belongs to azalide subclass of macrolide antibiotics and it composes of a 15-membered macrocyclic lactone ring. Gamithromycin has been developed for only veterinary medicine and is recommended at 6 mg/kg (SC) single dose in the prevention and/or treatment of *Mannheimia haemolytica*, *Pasteurella multocida* and *Histophilus somni* caused bovine respiratory disease in non-lactating dairy cattle. Macrolides show their antibacterial activity via inhibiting of protein biosynthesis. In the cattle, after 6 mg/kg (SC) injection, gamithromycin has long plasma elimination half-life (50 hours), large apparent volume of distribution (25 L/kg), higher bioavailability (~100%), quick and widespread distribution to lung tissue and prolonged lung tissue half-life. These characteristic pharmacokinetic values of gamithromycin are beneficial in the treatment of lung infections in cattle (EMEA 2009, Huang et al 2009, Baggott et al 2011). In the studies, it has been reported that administration of gamithromycin prior to *Mannheimia haemolytica* serotype A1 challenged calves has reduced the bacterial isolation from the lungs and severity of clinical signs of disease (Forbes et al 2011), and it has antimycoplasmal effect against to *Mycoplasma bovis* in non-lactating dairy cattle (Lechtenberg et al 2011).

Although gamithromycin was approved in the treatment of bovine respiratory disease in non-lactating dairy cattle by European Medicines Agency (EMEA 2009), drug may be used or suggested as extra-label in sheep (Strobel et al 2014), pigs (Wyns et al 2014), foals (Berghaus et al 2012) and broiler chicks (Watteyn et al 2013). According to pharmacokinetic research, single dose (6 mg/kg, SC) gamithromycin has been recommended in the sheep, and gamithromycin is suggested in the therapy of foot-rot in sheep (Kellermann et al 2014, Strobel et al 2014). Although gamithromycin may be used as extra-label in animals except for cattle, no detailed safety information is present, and commonly observed side effects of macrolide antibiotics are cardiotoxicity and hepatotoxicity (Andrade and Tulkens 2011, Yazar 2012).

Drugs have beneficial effect on the hosts, whereas they may have side effects and/or adverse drug reactions (Dogan 2011). Side effects of drugs on the system and/or organs may be determined some values measured from blood, serum and plasma. Troponin I and creatine kinase-MB mass (CK-MB mass) concentrations are evaluated for cardiac damage, while alkaline phosphatase (ALP), total bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma glutamyltransferase (GGT) and total protein levels are measured for the determination of bile duct and liver functions, on the other hand, blood urea nitrogen (BUN) and creatinine levels are evaluated for the determination of kidney function. Hemogram values [White blood cell counts (WBC), red blood cell counts (RBC), platelet, hemogram, he-

matocrit] reflects bone-marrow functions and fluid-electrolyte balance situation (Turgut 2000, Kerr 2002, Corum et al 2015).

In this research, it has been hypothesized that cardiotoxic effect of macrolide antibiotics is taken into consideration (Yazar 2012, Corum et al 2015), gamithromycin may show similar effect in sheep. In addition, gamithromycin may show the side effects on the other system/organs like other macrolide antibiotics (Andrade and Tulkens 2011, Yazar 2012).

The primarily aim of this research was to determine the effect of single dose (6 mg/kg, SC) gamithromycin on the specific cardiac damage markers (Troponin I and CK-MB mass) in sheep, in addition, to determine hepatic (ALP, total bilirubin, ALT, AST, GGT, total protein) and renal (BUN, creatinine) damage markers and hemogram (WBC, RBC, platelet, hemogram, hematocrit) values.

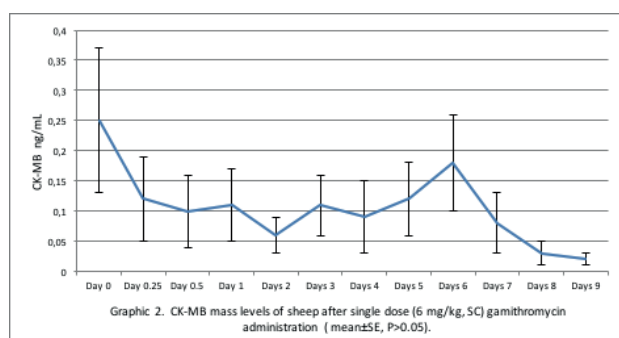
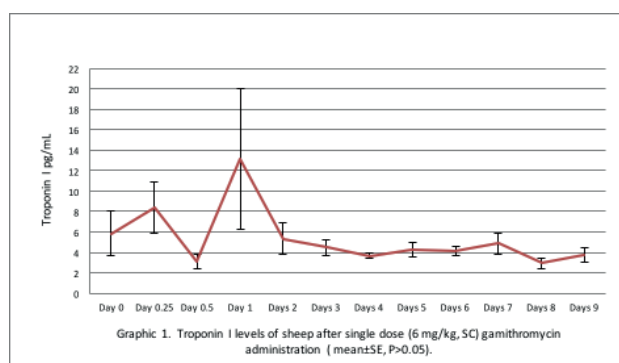
## Materials and Methods

Study protocol was approved by Ethic Committee of Veterinary Faculty, Selcuk University. Gamithromycin (Zactran® enj., Sanofi, Turkey) was administered as a single dose at 6 mg/kg subcutaneously to 10 Akkaraman sheep (>1 years 52.10±1.66 kg). Blood samples were taken before (Control, day 0) and after treatments at 0.25, 0.5, 1, 2, 3, 4, 5, 6, 7, 8 and 9 days. Specific cardiac damage markers (Troponin I and CK-MB mass) were measured by Siemens AdviaCentaur XP (Erlangen, Germany). Hepatic (ALP, total bilirubin, AST, ALT, GGT, total protein) and renal (BUN, creatinine) damage markers were determined by auto-analyzer (ILab-300 plus, Instrumentation Laboratory, Milano, Italy), while hemogram values (WBC, RBC, platelet, hematocrit, hemoglobin) were determined by hemocell counter (BC-2800 Auto Hematology Analyzer, Mindray Bio-Medical Electronics, Shenzhen, China).

Study results were presented mean ± SE. Data were evaluated ANOVA and Scheffe as posthoc test. P<0.05 level was accepted statistically significant.

## Results

Effect of gamithromycin on troponin I and CK-MB mass concentrations are shown in Graphic 1 and 2, respectively. Troponin I reached peak levels at first days after gamithromycin administration, but this difference was not statistically significant (P>0.05) within the days. There were any changes in the CK-MB mass levels, as well (P>0.05). Statistically significant fluctuations were determined (P<0.05) in the total bilirubin, total protein, creatinine and WBC levels, whereas no statistically significance were observed (P>0.05) in the other biochemical and hematological values (data not shown).



## Discussion

Gamithromycin is used or recommended in the some infections of sheep as extra-label drug (Kellermann et al 2014, Strobel et al 2014), although it has been recommended by European Medicines Agency in the treatment of bovine respiratory disease caused by *Mannheimia haemolytica*, *Pasteurella multocida* and *Histophilus somni* in non-lactating dairy cattle (EMA 2009).

In the current research, after gamithromycin administration, peak level of troponin I was determined at first day (24<sup>th</sup> hours), but this result was not statistically significant ( $P>0.05$ , Graphic 1), and there was no statistically significance changes determined ( $P>0.05$ ) in the CK-MB mass levels (Graphic 2). Blood CK-MB and troponin I levels are evaluated in the diagnosis of cardiac damage. Higher CK-MB and troponin I concentrations are detected within first 4 – 6 hours after myocardial infarction (Harrison and Amundson 2005, O'Brien 2008, Hallen 2012). Increased CK-MB mass and troponin I concentrations are used in the described of cardiac damage in sheep like humans (Ekici and Isik 2011, Er et al 2013). Cardiotoxic side effects of macrolide antibiotics are well known (Yazar et al 2001, Yazar 2012). Tilmicosin, a macrolide antibiotic, may cause death in lamb (Dogan 2011) and increases CK-MB and troponin I levels in rabbits (Yazar et al 2002). In addition, tulathromycin may increase CK-MB and troponin I levels in rabbits (Er et al 2011) and sheep (Corum et al 2015). When current research results related with cardiac damage markers are evaluated, it may be stated that gamithromycin has no distinctive cardiotoxic effect, though it has increased troponin I levels in sheep.

In the present study, gamithromycin caused statistically significant ( $P<0.05$ ) fluctuations in total bilirubin, total protein, creatinine and WBC levels. However, these results are within normal range reported about healthy sheep (Bulbul 2013, Corum et al 2015, Er et al 2015, Simsek et al 2015).

## Conclusion

It may be stated that administration of single dose gamithromycin (6 mg/kg, SC) do not cause cardiac damage, and it has no side effects on the liver and kidney functions and hemogram values in sheep. However, histopathological evaluations should be done to fully determination of gamithromycin safety in sheep.

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