# Combination of Trimethoprim - Sulfa methoxazole (Tr-SMZ) and Triplennamine (Trip) Induced QT Prolongation in Cattle

Mohammad mashayekhi[1*], Mohammad Amin Shahbazi[2], Mohsen Ahmadi Roozbahani[3]

1. Department of Clinical Sciences, Tabriz Branch, Islamic Azad University, Tabriz, Iran
2. Young Researchers club, Tabriz Branch, Islamic Azad University, Tabriz, Iran
3. Department of Veterinary, Kermanshah Branch, Islamic Azad University, Kermanshah, Iran
**Corresponding author:** TEL: +989144126030, Email address: Mashayekhi@iaut.ac.ir (Mohammad Mashayekhi)

**Abstract:** Trimethoprim (Tr) in combination with Sulfa methoxazole (SMZ) has a wide spectrum of activity against gram positive and negative organism. Although the popularity of using this drug because of its ease of administration noticeably has increased, numerous side effects of these drugs have been reported. Some of the most important of them are included: The skins, hematopoietic system, gastrointestinal tract, kidney and cardiotoxicity. Antihistamines are another cardio toxicity drugs that widely are prescribed in the world for treatment of allergic diseases. Histamines cause a series of action upon the cardiovascular system such as ventricular arrhythmia and QT prolongation by blocking rectifier potassium (k+) channels. However, co-administration of this drug with Tr-SMZ has become very popular for minor reasons in cattle. Unfortunately, there is no reliable source about cardio toxicity of these in QT prolongation. So the aim of this study was to assess the effects of Tr-SMZ with Trip on electrocardiographic criteria in Holstein cows.
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**Key words:** QT prolongation, Torsade De Pointes, Trimethoprim-Sulfamethoxazole, Triplennamine.

## 1. Introduction

It has been well recognized that many conditions may cause prolonged or abnormal repolarization (QT interval prolongation), which is associated with Torsade De Pointes (TDP) (Kannakeril et al., 2005). The term TDP refers to a ventricular tachycardia by QRS complexes of changing amplitude that appear to twist around the isoelectric line and it is characterized by prolonged QT repolarization (Libby et al., 2008). Many of non-cardiac drugs have been reported to cause QT prolongation and TDP (Paulussen et al., 2005; Justo et al., 2006). Two of the most important of these drugs in veterinary science are Tr-smz+Trip which both of them led to the development of early after depolarization with an apparently mechanism (Honig et al., 1992; Constanze et al., 2002; Justo et al., 2006; Libby et al., 2008). There are different kinds of k+ channels in the heart but two of them are more important for this matter which includes: Ikr (rapid) and Ks (slow). The Ikr is most susceptible to pharmacological influences. So blockage of the Ikr current causes a prolonged QT (i) and abnormalities on the surface of ECG. Prolonged repolarization causes activation of an inward depolarization current which is Early After Depolarization (EAD) with two types: phase2 (appearing at positive to -30 mv), phase3 (occurring at more negatives) (Honig et al., 1992; Tritanitirouzi et al., 2001; Constanze et al., 2002; Libby et al., 2008). Although both of them encountered in purkinje fibers, EADs activity recorded in ventricular are always phase 2 EADs. Afterwards of this phenomenon, dispersion of repolarizations may induce reentry and stimulate TDP which is acquired polymorphic tachycardia. If TDP is rapid or prolonged, it can lead to ventricular fibrillation and sudden cardiac death. Essentially TDP may be caused by either congenital or acquired, which has been explained previously, long QT syndrome (LQTS) which is disease of ventricular depolarization identified by prolongation of QT interval on ECG. (Honig et al., 1992; Constanze et al., 2002; Paulussen et al., 2005; Justo et al., 2006; Libby et al., 2008).

## 2. Materials and Methods

Ten clinically healthy Holstein cows (5 non pregnant female and 5 male cows in average of 5 years old and weight of 450 ± 25kg) were selected randomly for this study. The female cows were dried off. There were no parasitic infestations in them according to the para clinical examination in the Department of Veterinary Clinical Pathology. In this study we used ECG set (Cardimax, model: Fx-2111), 2-Trimethoprim-Sulfamethoxazole (intertri, manufactured by inter chemie werken "De adelaar" B.V. metaatwey8venary.holland) that each vial is contained: 100mlSMZ 200mg+Tr40mg perml.3-Triplennamine (manufactured by Nasr pharmaceutical Co.) that each vial is contained: 25ml Triplennamine HCL 25mg per ml.

All of the cows were examined sequentially for two days before administrating to evaluate their cardiac and lung health by auscultation, electrocardiographing. Their diets were not changed during this experiment. Afterwards, Intertrim (1mL per 10 kg twice a day for 5 days intramuscularly) and Triplennamine(1mL per 25 kg once a day for 5 days intramuscularly) were injected . At the end of this protocol the animals were kept in a quiet and free distraction area. Then, an ECG with speed of 25 mm/s, voltage of 50 Hz was taken from all the cows in a non-stressful condition without any chemical restraining drugs. Then, the base apex (apex base) technique was used to record ECG in lead I. All ECGs were compared with reference values and carefully by measuring of - Heart rate, P R-interval, A- amplitude, P- duration, QRS duration, R - amplitude, S-T segment, QT- interval, QT corrected (Bazzet's formula). Additionally, they were issued about different arrhythmias too.

### 2.1. Statistical analysis

Data were analyzed by paired sample T Test for Heart rate, P R-interval, P- amplitude, P- duration, QRS duration, R - amplitude, QT interval (QTi), QT corrected (QTc) and normal Q Q plot for (QTi), (QTc) plus Histogram graphs for (QTi), (QTc) before and after drug administration using spss version 19.

## 3. Results

The results showed that the cows were normal according to their heart and lung sounds but two of them had biphasic T waves in their electrocardiogram during two days before drug administration (Figure 1). In this study there were significantly statistical differences ($P < 0.01$) in QT prolongation and heart rate before and after drug administration (Figures 2, 3).The results of the means ± standard deviations and p values are recapitulated in Table 1 and the graphs are shown in figure 4. TDP were not observed in our investigation because of utilizing recommended dosage of drugs.

**Table 1:** Electrographic criterias before (on day 0) and after (on day 5) drug administration

| Parameter | Day 0 | Day 5 | *P* value |
|---|---|---|---|
| Heart rate | 66.50 ± 7.13 | 80.70 ± 12.32 | [a] 0.004 |
| P- R interval | 0.174 ± 0.018 | 0.176 ± 0.020 | 0.78 |
| P amplitude | 0.950 ± 0.049 | 0.950 ± 0.036 | 1.00 |
| P duration | 0.069 ± 0.017 | 0.080 ± 0.000 | 0.084 |
| QRS duration | 0.066 ± 0.018 | 0.072 ± 0.013 | 0.394 |
| R amplitude | 0.610 ± 0.237 | 0.540 ± 0.117 | 0.373 |
| Q-T interval | 0.365 ± 0.037 | 0.419 ± 0.025 | [a] 0.0001 |
| Q-T corrected | 0.385 ± 0.041 | 0.489 ± 0.032 | [a] 0.0001 |

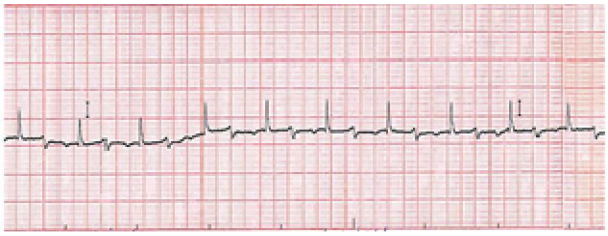

**Figure 1:** Electrocardiogram of a female cow before drug administration's shows biphasic T wave.

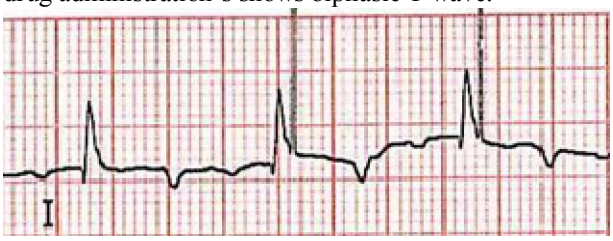

**Figure 2:** Electrocardiogram of female cow before drug administrations.

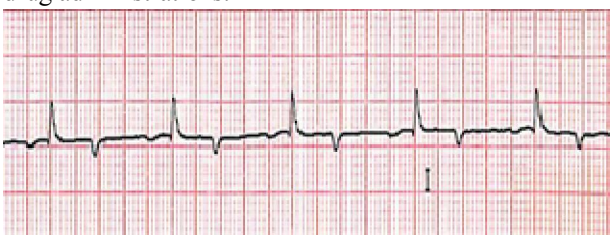

**Figure 3:** Electrocardiogram of female cow after drug administrations.

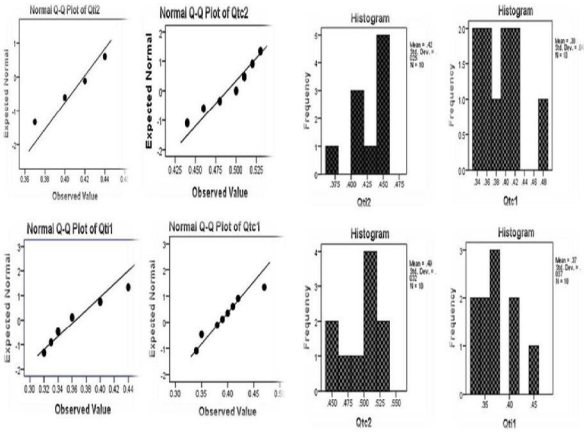


**Figure 4:** the bar charts demonstrate some information given about two types of QT interval. One of them is non-corrected QTi and the other one has dedicated the corrected one. Conspicuously, although both of them represent the same concepts, fluctuated numbers for QTi and QTc are noticeably discrepant so that, QTi before and after administrations are alternated around 0.33 to 0.45. On the contrary, QTc devote numbers approximately from 0.34 to 0.52. More importantly, the graphs QTi2 is focused around 0.4 to 0.45 while QTi1 is fluctuated close 0.32 to 0.36. Furthermore, Qtc1= 0.34 to 0.42 and QTc2= 0.45 to 0.53.

## 4. Discussion

Long QT syndrome is characterized by prolonged ventricular repolarization and a high risk of malignant ventricular tachyarrhythmia. This syndrome can be divided into congenital and acquired forms (Libby et al., 2008). Induced or acquired long QT is iatrogenic, caused by some of medications like: some of antibiotics and antihistamins (Libby et al., 2008). A large number of factors determine the risk of developing long QT syndrome in an individual in response to drug therapy. They include bioavailability of the drug, the interaction with other medications that affect the same repolarizing current. The final effect on the repolarization will depend on the so-called repolarizing reserve, or the degree of alteration that the ionic currents can sustain before repolarization is compromised. Any combination of genetic and environmental factors (drug, electrolyte abnormalities) that decrease this "repolarization reserve" below a safe threshold will place the individual at risk of arrhythmia (O'Rourke et al., 2009). Although data suggest a genotype-phenotype correlation in this arrhythmia (Libby et al., 2008; O'Rourke et al., 2009). The acquired form has a long-QT interval caused by various drugs (Libby et al., 2008). In fact LQT syndrome is recognized as a group of ion channel diseases (Kaneko et al., 1999; Libby et al., 2008., O'Rourke et al., 2009). Abnormal repolarization (QT interval prolongation) is occurred during administration of some drugs in the cows. It has been shown that combination of Trimethoprim with Sulfa methoxazole and antihistamines result in alter cardiac repolarization leading to QTc interval prolongation and torsades de pointes (Honig et al., 1992; Usui et al., 1998; Constanze et al., 2002; Rezakhani et al., 2004; Justo et al., 2006; Libby et al., 2008; O'Rourke et al., 2009). In this study a significant Qt prolongation and increased heart rate were happened after drugs administration. Sulfonamides are bacteriostatic agents while trimethoprim is bactericidal, but in combination, the potentiated sulfas are bactericidal (Anthony et al., 2007). Potentiated sulfas sequentially inhibit enzymes in the folic acid pathway, thereby inhibiting bacterial thymidine synthesis. The sulfonamide blocks the conversion of para-aminobenzoic acid (PABA) to dihydrofolic acid (DFA), and trimethoprim blocks the conversion of DFA to tetrahydro¬folic acid by inhibiting dihydrofolate reductase (Justo et al., 2006; Anthony et al., 2007). Interestingly enough, although sulfas have a fairly broad spectrum of activity against organisms (Anthony et al., 2007) and they are used with antihistamines to reduce inflammatory situations, there are plenty of side effects such as cardio toxicities. Hence, the chance of provoking a fatal arrhythmia (TDP) as the result of taking a ‘‘harmless’’ these agents is very troubling and despite the fact that several risk factors for its occurrence have been reported such as; female gender and older cases, advanced heart disease, hypokalemia, digitalis therapy, concomitant use of an inhibitor of hepatic drug metabolism (Justo et al., 2006; Anthony et al., 2007), the most effective one is female gender (Paulussen et al., 2005). To put it in a nutshell, although the Food and Drug Administration has recently issued warning letters to veterinarians for their illegal use of sulfamethoxazole and not paying attention to withdrawal time by them, it is essential to urge physicians to prescribe antibiotics only after careful clinical evaluation of risk factors for QT prolongation and TDP, and when they want to add antihistamines. Moreover, Usui et al (1998) recorded similar finding in early after depolarization in vivo canine model by administration of terfenadine (Usui et al., 1998). Yee Guan Yap and A John Camm (2003) reported a significant increase in QT prolongation by administration of antihistamines and antibiotics. Finally, roden et al. (2005) showed that administration of these drugs blocks cardiac Ikr(5).

In conclusion, the results of this study showed prolonged QT by administration of Tr-SMZ in combination with Triplennamine become more questionable as a routine treatment in cows.

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