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Full Length Research Paper

Tulathromycin disturbs blood oxidative and coagulation status

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The aim of this study was to determine the effect of tulathromycin on serum oxidative status and coagulation factors in rabbits. Tulathromycin was administered to eight rabbits, and blood samples were obtained 0, 1, 5, 10 and 15 days after treatment. Indicators of serum oxidative status (malondialdehyde, nitric oxide, superoxide dismutase, retinol and β-carotene) and coagulation values (antithrombin III, fibrinogen) were measured after tulathromycin treatment. In addition, routine serum biochemical values (creatine kinase-MB, lactate dehydrogenase, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, gamma glutamyl transferase, creatinine, blood urea nitrogen, cholesterol, triglyceride, high density lipoprotein, amylase, total protein, albumin, glucose and calcium), haemacell counts (white and red blood cells) and arterial blood gas parameters (packed cell volume, hemoglobin, pH, partial pressure of carbon dioxide, partial pressure of oxygen, actual bicarbonate, standard bicarbonate, total carbon dioxide, base excess *in vivo*, base excess *in vitro*, oxygen saturation, sodium and potassium) were also determined. Tulathromycin increased ($P < 0.05$) the levels of malondialdehyde, nitric oxide and superoxide dismutase activity, and decreased ($P < 0.05$) the level of antithrombin III. In conclusion, tulathromycin may cause oxidative damage and coagulation disorders during the treatment period.

Key words: Tulathromycin, oxidative damage, coagulation disorder.

INTRODUCTION

Macrolide antibiotics are antibacterial agents that are widely used in the treatment of infections of the respiratory piratory system, soft tissue and skin in humans and domestic animals. Macrolide antibiotics are usually bacteriostatic. They inhibit protein synthesis via reversible binding to the 50S ribosomal RNA of susceptible micro-organisms. Clarithromycin and azithromycin are mostly prescribed for humans, whereas tylosine, tilmicosine and tulathromycin are mostly prescribed for animals. Tulathromycin is a new member of the triamilide subclass of macrolide antibiotics. After administration of a single dose, it may be retained in the lung (the target organ) for

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Abbreviations: ROS, Reactive oxygen species; **NO,** nitric oxide; **SOD,** superoxide dismutase; **MDA,** malondialdehyde; **NOS,** nitric oxide synthase; **AT,** antithrombin III.

up to 9 days (Anadon and Reeve-Johnson, 1999; Abu-Gharbieh et al., 2004; Yazar, 2009).

Cells require a physiologic concentration of oxygen to maintain life, but oxygen may generate destructive derivatives named reactive oxygen species (ROS) (Gupta et al., 2007). The best known oxygen-derived ROS are the superoxide anion, hydroxyl radical, hydrogen peroxide, nitric oxide (NO) and peroxynitrite. The body is protected by its antioxidants against damage caused by ROS. A balance develops between the production of ROS and both enzymatic (superoxide dismutase (SOD), glutathione peroxidase, catalase, etc.) and nonenzymatic (glutathione and vitamins A, E and C) antioxidants under normal physiological states. Oxidative damage develops when this balance is disrupted by extreme generation of ROS and/or insufficient antioxidant capacity (Salvemini and Cuzzocrea, 2002; Macdonald et al., 2003). Oxidative damage causes lipid peroxidation. SOD catalyzes the dismutation of two superoxide radicals to molecular oxygen and water. Measurement of malondialdehyde (MDA) is accepted as a basic test of lipid peroxidation in clinical settings worldwide (Salvemini and Cuzzocrea, 2002; Berger and Chiolero, 2007).

NO is an oxygen-derived free radical that is produced by NO synthase (NOS). At least three distinct isoforms of NOS exist in mammalian cells: endothelial, neuronal, and inducible NOS (iNOS). Endothelial and neuronal NOS are expressed constitutively, whereas iNOS is induced; it produces large quantities of $NO^{\cdot}$, and the formation of high levels of NO^{-} produces peroxynitrite. The combination of NO^{-} and peroxynitrite may cause hypotension, cytotoxicity and tissue damage (Stoclet et al., 1999).

Coagulation is controlled by procoagulant and anticoagulant mechanisms in the blood. Factor Xa converts prothrombin to thrombin, and thrombin stimulates the conversion of fibrinogen to fibrin. Thus, formation of blood clot may occur. Two anticoagulant defense mechanisms are present in the blood, a direct protease inhibitor system that includes antithrombin III (AT) and tissue factor pathway inhibitor, and an indirect system that consists of protein C (Spronk et al., 2003; Zeerleder et al., 2005).

The effects of macrolide antibiotics on oxidative (Yazar et al., 2002a, 2004; Ueno et al., 2005; Kumar et al., 2008), coagulation status (Purdy et al., 2002; Bouwman et al., 2004) and organ damage markers (Er and Yazar, 2010) have been investigated in healthy and sick individuals. However, to the best of our knowledge, the effect of tulathromycin on the oxidative and coagulation status of the blood has not been researched.

The aim of the present study was to investigate the effect of tulathromycin on serum oxidative and plasma coagulation status, and also to investigate its effect on routine serum biochemical values, haemacell counts and arterial blood gas parameters.

MATERIALS AND METHODS

Animals and experimental design

Eight male New Zealand white rabbits (18 to 24 months, 2900 to 3600 g) from Experimental Medicine, Research and Application Center, Selcuk University, Konya, Turkey were used and the study protocol was approved by the Ethics Committee of the Veterinary Faculty. The animals were fed a standard pellet diet and tap water *ad libitum*. Tulathromycin (Draxxin inj, Pfizer Animal Health, Istanbul, Turkey) was given as a single subcutaneous (SC) injection at 10 mg/kg body weight. After the treatment, blood samples were collected from the auricular artery at 0, 1, 5, 10 and 15 days.

Analysis of values

Serum levels of MDA (Drapper et al., 1986), NO (Miranda et al., 2001), SOD (Sun et al., 1988), retinol and β-carotene (Suzuki and Katoh, 1990) were measured, using methods published previously, with an enzyme-linked immunosorbent assay/spectrophotometric reader (MWGt Lambda Scan 200, Bio-Tek Instruments, VT, USA).

Citrated plasma antithrombin III and fibrinogen levels were determined with an auto-analyzer (Siemens Dade Behring, Deerfield, IL, USA). Serum levels of creatine kinase-MB (CK-MB), lactate dehydrogenase (LDH), alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma glutamyl transferase (GGT), creatinine, blood urea nitrogen (BUN), cholesterol, triglyceride, high density lipoprotein (HDL), amylase, total protein, albumin, glucose and calcium were measured with an auto-analyzer (ILab-300 Biomeriux Diagnostic, Milano, Italy). White blood cell (WBC) and red blood cell (RBC) counts were determined with a hemocytometer. The packed cell volume (PCV), hemoglobin (Hb), pH, partial pressure of carbon dioxide (pCO_2), partial pressure of oxygen (pO_2), actual bicarbonate (HCO_3^{-}), standard bicarbonate (HCO_3 std), total carbon dioxide (tCO_2), base excess *in vivo* (Be_{vv}), base excess *in vitro* (Be_{vt}), oxygen saturation (O_2 sat), sodium (Na) and potassium (K) levels were measured in heparinized blood using a blood gas analyzer (GEM Premier Plus, IL, USA).

Statistical analysis

All values are expressed as mean ± SE. The results were analyzed by ANOVA and Duncan's multiple range test (SPSS for Windows 12.0). In all cases, a probability of error less than 0.05 was selected as the criterion for statistical significance.

RESULTS

The serum oxidative and plasma coagulation status is given in Table 1, while the routine serum biochemical values and haemacell counts, plus arterial blood gas parameters, are shown in Tables 2 and 3, respectively. Tulathromycin increased ($P < 0.05$) the levels of MDA, NO, SOD and CK-MB, and decreased ($P < 0.05$) the level of AT. Although, statistically significant changes were determined in the levels of creatinine, calcium, PCV and Hb, these changes were within normal values. No clinical abnormalities were observed after drug administration.

Table 1. Serum oxidative and plasma coagulation status of tulathromycin treated rabbits (mean±SE).

Parameter	0 day	1 day	5 day	10 day	15 day
MDA (mM)	3.17±0.30^{b}	4.36±0.26^{a}	4.40±0.14^{a}	3.78±0.29^{ab}	3.57±0.44^{ab}
NO (µM)	7.68±1.23^{bc}	11.6±1.71^{a}	10.7±1.45^{ab}	5.72±0.64^{c}	4.38±0.76^{c}
SOD (µg/L)	90.1±8.7b^{b}	119±17.8^{ab}	106±13.3^{ab}	141±7.69^{a}	98.7±10.5^{ab}
RT (µg/L)	25.8±1.46	27.2±1.25	23.1±1.37	24.3±1.44	23.4±0.99
βC (µg/L)	0.63±0.07	0.52±0.05	0.65±0.03	0.69±0.05	0.63±0.06
AT (%)	119±9.59^{a}	60.1±7.00^{b}	59.8±6.34^{b}	83.1±13.6^{b}	113±9.69^{a}
Fibrinogen (mg/dL)	196±9.82	199±26.0	211±18.2	204±18.3	213±15.5

$^{a, b, c}$: Different letters in the same line are statistically significant (Duncan's multiple range test, $P < 0.05$).

Table 2. Routine serum biochemical values of tulathromycin treated rabbits (mean±SE).

Parameter	0 day	1 day	5 day	10 day	15 day
CK-MB (U/L)	1034±160^{b}	4420±560^{a}	803±119^{b}	565±70.1^{b}	704±149^{b}
LDH (U/L)	128±24.1	99.4±18.3	79.9±32.4	99.6±19.6	75.3±14.4
ALP (U/L)	48.9±10.4	39.3±11.1	36.1±9.57	39.4±7.94	41.3±7.36
ALT (U/L)	40.6±5.63	38.0±3.51	36.4±2.28	39.8±5.76	47.1±6.61
AST (U/L)	26.0±4.96	19.6±2.28	18.1±2.92	18.1±3.52	30.1±6.69
GGT (U/L)	7.13±0.81	6.63±0.71	6.25±0.86	7.13±1.34	6.88±1.04
CR (mg/dL)	0.90±0.09^{b}	1.13±0.11^{ab}	1.33±0.07^{a}	1.26±0.15^{a}	1.14±0.07^{ab}
BUN (mg/dL)	39.4±2.74	37.6±2.27	33.8±1.22	41.0±5.26	40.9±3.05
CH (mg/dL)	59.6±2.87	61.4±8.05	55.1±4.18	59.1±10.2	61.9±9.59
TR (g/dL)	127±23.6	167±27.5	184±36.2	131±22.9	132±26.7
HDL (mg/dL)	14.0±2.43	14.9±1.88	12.9±2.48	13.9±3.10	16.9±3.81
AML (U/L)	221±13.4	228±17.6	263±20.3	233±22.1	249±21.0
TP (g/dL)	6.70±0.46	6.38±0.28	6.29±0.32	6.45±0.68	6.19±0.36
ALB (g/dL)	4.55±0.27	4.25±0.15	4.00±0.09	4.19±0.31	4.13±0.19
GLU (mg/dL)	110±6.04	141±14.9	129±8.79	130±11.1	125±6.25
Ca (mg/dL)	11.4±1.11^{b}	12.3±1.00^{ab}	14.4±0.61^{a}	14.1±1.09^{ab}	14.4±0.59^{a}

$^{a, b}$; Different letters in the same line are statistically significant (Duncan's multiple range test, $P < 0.05$).

DISCUSSION

Macrolide antibiotics are the most commonly prescribed drugs in humans and domestic animals. Tulathromycin, a relatively new macrolide antibiotic, is used especially in the treatment of respiratory disease. It may be retained in the lung for many days after administration of a single dose (Anadon and Reeve-Johnson, 1999; Abu-Gharbieh et al., 2004; Yazar, 2009).

Tulathromycin increased ($P < 0.05$) the levels of serum MDA and SOD (Table 1). The effects of macrolide antibiotics on antioxidant status have been reported previously. Tilmicosin, another macrolide antibiotic, increased the level of MDA (Yazar et al., 2004; Kart et al., 2007) and decreased SOD activity (Yazar et al., 2002a). Increased SOD activity may be derived from oxidative stress. In contrast, erythromycin, azithromycin, roxithromycin and clarithromycin decreased the level of MDA (Aktan et al., 2003). The results of studies of antioxidant activity in which only antioxidant enzymes are evaluated are in disagreement with other studies. However, when MDA is evaluated as an indicator of oxidative damage, consistent results have been obtained (Konyalioglu et al., 2007; Er et al., 2010a; Yazar et al., 2010). It is generally accepted that the macrolides used in human medicine have antioxidant effects. However, tulathromycin is a member of the triamilide subclass of macrolide antibiotics, which cause oxidative damage. Different effects of macrolide antibiotics on oxidative status may be the result of differences in dose or the molecular structure of the drugs.

Tulathromycin increased ($P < 0.05$) the level of NO (Table 1). It has been reported that erythromycin, azithromycin, roxithromycin and clarithromycin increase NOS

Table 3. Hemacell counts and arterial blood gas values of tulathromycin treated rabbits (mean±SE).

Parameter	0 day	1 day	5 day	10 day	15 day
WBC x10^3 (µL)	6.84±0.64	9.08±0.91	7.71±0.66	7.86±0.60	7.89±0.82
RBC x10^6 (µL)	7.04±0.47	6.30±0.37	7.36±0.56	6.99±0.55	7.66±0.61
PCV (%)	34.8±0.84^{b}	38.5±2.10^{ab}	34.4±1.58^{b}	40.8±3.22^{ab}	41.6±1.84^{a}
Hb (g/dL)	11.0±0.24^{ab}	11.9±0.65^{ab}	10.7±0.49^{b}	12.6±1.00^{ab}	12.9±0.57^{a}
pH	7.44±0.01	7.45±0.03	7.41±0.02	7.40±0.02	7.42±0.02
pCO_2 (mmHg)	27.8±0.86	26.3±2.39	26.5±1.92	26.3±1.41	29.3±1.38
pO_2 (mmHg)	87.9±4.38	92.9±11.3	94.4±12.5	89.6±5.64	80.1±2.88
HCO_3^- (mmol/L)	18.7±0.55	18.6±1.81	16.9±1.14	16.6±0.90	19.0±0.74
HCO_3 (std)	21.5±0.48	21.6±1.46	19.8±0.99	19.5±1.09	21.6±0.65
tCO_2 (mmol/L)	19.5±0.57	19.4±1.87	17.7±1.20	17.3±1.27	19.9±0.76
Be_{vv} (mmol/L)	-5.60±0.66	-5.38±2.05	-7.79±1.22	-8.38±1.50	-5.38±0.89
Be_{vt} (mmol/L)	-4.54±0.59	-4.20±1.86	-6.60±1.28	-6.95±1.41	-4.24±0.83
O_2 sat (%)	96.9±0.35	96.4±1.10	96.3±0.65	96.6±0.41	95.9±0.77
Na (mmol/L)	151±2.05	147±2.78	150±2.83	150±2.34	148±1.79
K (mmol/L)	3.54±0.05	3.63±0.20	3.58±0.17	4.05±0.19	3.90±0.15

$^{a, b}$: Different letters in the same line are statistically significant (Duncan's multiple range test, $P < 0.05$).

activity (Aktan et al., 2003). NO/peroxynitrite, a member of ROS, may cause cytotoxicity and tissue damage. Following oxidative tissue damage caused by ROS, increased levels of MDA may be observed (Stoclet et al., 1999; Berger and Chiolero, 2007). In this study, increased levels of MDA and NO were determined simultaneously (Table 1). When the expression of nuclear factor kappaB (NF-κB), a ubiquitous transcription factor, is stimulated by various agents, over expression of inflammatory mediators (cytokines, iNOS) may be observed (Macdonald et al., 2003). The effects of macrolide antibiotics on the inflammatory mediators have been reported previously (Er et al., 2010b; Uney et al., 2010). The overproduction of NO that results from induction of NF-κB by tulathromycin may cause oxidative damage. However, further investigations are required to determine the specific cellular target of tulathromycin.

Tulathromycin decreased ($P < 0.05$) the level of AT, whereas, it had no effect on the concentration of fibrinogen in the rabbits studied (Table 1). Studies have shown that macrolide antibiotics have no effect on the synthesis of fibrinogen (Purdy et al., 2002; Bouwman et al., 2004). The effect of macrolide antibiotics on the concentration of AT has not been reported in the literature. However, macrolide antibiotics are metabolized by the liver (Yazar, 2009) and it may be assumed that tulathromycin depresses the synthesis of AT in the liver.

Tulathromycin increased ($P < 0.05$) the activity of CK-MB on the first day after treatment (Table 2). Although, macrolide antibiotics are generally well tolerated by users, cardiotoxicity is a seldom observed but serious side effect (Anadon and Reeve-Johnson, 1999; Abu-Gharbieh et al., 2004). Creatine kinase produces adenosine triphosphate which is an important energy source for many tissues including the heart. It has three different isoenzymes: CK-MM, CK-BB and CK-MB. CK-MB comprises 15 to 30% of the total CK activity in the heart. CK-MB is released by damaged heart tissue and is a favored diagnostic marker for acute myocardial infarction (Robinson and Christenson, 1999; Fromm, 2007). Cardiotoxcity is a significant limiting factor in the use of drugs. Cardiotoxic drugs may cause prolongation of the QT interval or arrhythmias that predispose to torsade de pointes, via direct interaction with the ion channels of the heart (O'Brain, 2008). When macrolide antibiotics cause prolongation of the QT interval and fatal ventricular arrhythmias, increased activities of CK and CK-MB have been reported (Yazar et al., 2002b; Von Essen et al., 2003; Abu-Gharbieh et al., 2004; Fromm, 2007; Kart et al., 2007). This effect of tulathromycin may depend on blockage of K^+ channels, as with other macrolides.

Tulathromycin caused statistically significant ($P < 0.05$) changes in routine serum biochemical (Table 2) and hematological (Table 3) parameters. However, these changes were within normal limits. Changes within normal limits caused by macrolide antibiotics have been reported previously in experimental studies (Altunok et al., 2002; Yazar et al., 2004).

In conclusion, tulathromycin may cause disorders in oxidative stress and coagulation status. These effects

may be more important in patients with coagulation disorders.

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