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Effect of a macrolide antibiotic "tulathromycin" on the fertility of male albino rats

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Abstract

The aim of the present study was to study the effects of tulathromycin on the fertility of male rats indicated by evaluation of semen picture, measuring the testosterone level and pathologic changes of testes. The later included routine histopathologic examination as well as morphometric analyses of seminefrous tubules and epididymal duct diameters. Thirty apparently healthy adult Albino male rats (average weight 160-200 g) were allocated into 3 equal groups (n=10). Rats of the first group was kept as control and injected with 0.1 ml normal saline subcutaneously once weekly for three successive weeks. The animals of the second group were subcutaneously injected with tulathromycin in a dose of 2.5 mg/kg B.wt twice with 15 days interval, and the third group were subcutaneously injected with tulathromycin (2.5mg/kg b.wt) for three successive weeks. Rats were sacrificed at 65 days of treatment and testes and epididymes were removed, weighted and histopathologically examined. Results revealed that tulathromycin administration significantly ($p<0.0001$) decreased the weight of testes and epididymes and adversely affect the semen quality (decreased sperm cell count and motility and increased abnormalities). Testesterone level was significantly ($p<0.0001$) deceased. Histopathological examination revealed that, degenerative changes of spermatogenic cells and reduction in numbers of spermatozoa in the central lumen of seminiferous and epidydimal tubules were found in groups treated with tulathromycin. Statistically, a significant differences between injected and control groups were detected using morphometric analyses of seminefrous tubules and epidydimal ducts diameter, indicating that tulathromycin pose a negative effect on the histology of the testes. It could be concluded that fertility of rats was adversely affected by repeated injection of tulathromycin in a therapeutic dose of (2.5 mg/kg b.wt).

Key words: Tulathromycin, fertility, testosterone, histopathology, morphometric, rats.

Introduction

Several decades ago, antibiotics are widely used for prevention, treatment and control of diseases in both animal and poultry aiming to optimize the production and increase the size of live stock. However, some of them were known to cause, infertility or significant alterations in semen, some biochemical dysfunctions and might induce testicular damage to animal and human (Schlegel et al., 1991). For example, the use of nitrofuranation and sulfasalazine, has been demonstrated to cause oligospermia, poor sperm motility and decrease seminal quality. Moreover, tetracycline hydrochloride, antibiotics in the penicillin group (Penicillin-G,

ampicillin and dicloxacin) and macrolide group (erythromycin, spiramycin and neomycin) have been used studying the negative effect on male fertility (Olayemi, 2010).

Macrolide antibiotics, active agents against Gram-positive bacteria, are frequently used, curative or prophylactic aim, as veterinary drugs in food-producing animals (Leal et al., 2001) . Newer macrolides, such as tulathromycin, have been designed with modified configuration to enhance in vitro and in vivo antibacterial properties along with increasing the bioavailability, better tissue penetration, and extended tissue half lives (Benchaoui et al., 2004). Tulathromycin, a triamilide macrolide antimicrobial drug, was found to be effective against swine and cattle respiratory bacterial agents, has been identified as a potentially useful drug in caprines (Clothier et al., 2012) and more efficacious injectable macrolide antibiotic used for the treatment of pneumonia of ruminants compared with other antibiotics in recent years (Venner et al., 2007). It acts by binding to the 50 small ribosomal subunit to prevent translocation of the growing peptide and blocking protein synthesis (Benchaoui et al., 2004).

Little is known about tulathromycin effect on the male fertility. Initially, it has been reported that it has an adverse effect on the male fertility when given in high doses. Thus the aim of this study was to investigate the effect of repeated administration of the therapeutic dose of tulathromycin, antibiotic on male rats fertility, serum testosterone level, testes and epididymes weights and pathologic changes of the testes and epididymes.

Material and Method

Drug

Tulathromycin (100mg/ml) was supplied as an injectable solution (Draxxin®) by Animal Health Division Pfizer Company, Cairo, Egypt.

Experimental animals

Thirty apparently healthy adult Albino male rats (Average weight 160-200g) were obtained from breeding unit of Helwan farm of laboratory animals (Helwan, Egypt). Rats were caged in groups and fed a commercially prepared pellet diet and watered ad libitum throughout the study.

Experimental design

After 2 weeks of acclimatization, rats were equally divided into three equal groups (n=10). The first group (C) were subcutaneously injected with 0.1ml normal saline once weekly for three weeks and kept as (control group). The rats of the second group (G1) were subcutaneously injected with tulathromycin in a dose of (2.5mg/kg b.wt) twice with 15 day interval (Er and Yazar, 2010). The third group (G2) were subcutaneously injected with tulathromycin (2.5mg/kg b.wt) for three successive weeks. Duration of the experiment was 65 days to complete time of one spermatogenesis and maturation of sperms in epididymes (Jackson, 1966). Animals

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were weighed and sacrificed at 65days of treatment.

Blood samples

Blood samples were collected from the retro-orbital venousplexus (poole, 1987), using clean microcapillary tubes. Collected blood was put in a clean screw-capped bottle and then incubated at 37°C until clotting, centrifuged at 3000 rpm for 15 min to obtain serum which is stored at -20°C till use.

Reproductive organ weights

All male rats were weighted and sacrificed. Testes and epididymes were dissected out and weighted. The relative weight of testes and epididymes were calculated using the following equation (Hala et al., 2012):

$$\frac{\text{Organ weight (g)}}{\text{The corresponding total body weight}} \times 100$$

Semen evaluation

Semen samples were collected by maceration of epididymes to measure sperm count and motility (Narayana et al., 2005). Semen smears were made and stained with 1% eosin to measure sperm count by using haemocytometer and semen film was prepared and stained by Eosin-Nigrosin stain and examine under a light microscope to determine the live/dead percentage and sperm abnormalities. The sperm abnormalities are classified according to their origin into primary abnormalities (gaint or dwarf head, double head, double tail and/or coiled tail) and secondary abnormalities (detached head, bent and/or wavy tail) (Bearden and Fuqucy, 1980).

Hormone assay:

Estimation of serum testosterone level was performed using Enzyme immunoassay for the quantitative determination of testosterone (Chemux Biocience, Inc, south San Francisco, CA94080, USA) (Chen et al.,1991).

Pathologic investigations

a. Routine histopathogy

Testes and epididymes were bisected and the sagittal plane was fixed in 10% neutral buffered formalin. Samples were routinely processed and embedded in paraffin wax. Sections (5 µm) were stained with HE (El-Habashi et al., 2010).

b. Morphometric analyses of seminiferous and epididymal ducts:

For image analysis, a freeware version of Image-J 1.48v downloaded from the NIH website (http://rsb.info.nih.gov/ij) was used to measure (in microns) the diameter of seminiferous and epididymal ducts using HE-stained sections .Ten random fields from both testes of each animal were selected to measure changes in seminiferous tubules (Batra et al., 2001). From each rat, twenty tubular profiles that were almost rounded were randomly chosen and measured. The tubular diameter was determined and expressed in μm at 200 x magnification.

Statistical analysis

Data of fertility studies were statistically analyzed as a complete randomized design using one-way ANOVA. Significant differences among individual treatment means were determined using Tukey's test (SPSS 20 the least square analysis procedure). Data of morphometric analysis were statistically analyzed using Minitab Statistical Software (MTW13) and Microsoft excel. General Linear Model (GLM) was used to quantify the significance between seminiferous tubules and epididymal duct diameters in different groups. $P<0.05$ was considered as statistically significant..

Results

1-Parameters of fertility

Subcutaneous administration of tulathromycin (2.5mg/kg b.wt) to male rats in the 2nd and 3rd groups induced significant decrease in sperm cell count , motility and increase in sperm abnormalities($P<0.001$) as shown in (Table 1). A significant decrease in testes and epididymes weights ($P<0.0001$) occurred among treated groups (Tables 2, 3).

2-Serum testosterone levels

The current study showed that administration of tulathromycin resulted in significant decrease in serum testosterone levels ($P<0.0001$) in both the 2nd and 3rd groups (0.25 and 0.21ng/ml) as compared with the corresponding control values (2.1ng/ml) as illustrated in (Table 3).

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Table (1): Effect of tulathromycin administration on semen picture of rats in both treated and control groups (mean ± SE).

Groups	Semen picture					
	Motility (%)	Count ($\times 10^6$)	Live/ dead (%)		Abnormalities (%)	
			Live	Dead	Primary	Secondary
Control	86.4±1.4	1.04±4.4	73.8±2.2	27.2±1.9	1.4±0.3	8.7±1.4
G1	18.3±4.0***	0.2±2.7***	42.0±6.9***	48.5±4.8***	2.0±0.7	32.9±7.2***
G2	30.6±2.4***	0.19±1.4***	52.0±1.9***	44.0±1.1***	2.4±0.4	29.3±0.5***

*** values within column were significantly differ at $P < 0.0001$

Table (2): Influence of tulathromycin administration on weight of testes and epididymes diameters of seminiferous tubules and epididymal duct (µm) of treated and control groups (g), (mean ± SE).

Groups	Weight of testes	Seminiferous tubule diameter	Weight of epididymes	Epididymal duct diameter
Control	1.38±1.70	271.83 ± 42.76	0.34±1.20	192.37±28.89
G1	0.46±1.90***	238.11 ± 44.32 **	0.19±1.69***	146.44±32.65***
G2	0.60±8.40***	207.91 ± 62.43 **	0.22±1.57**	150.03±34.85***

values within column were significantly differ at *** $P < 0.0001$, ** $P < 0.00$

Table (3): Relative weight (g) of testes and epididymes and serum testosterone level (ng/ml) in rats of tulathromycin-treated and control groups (mean ± SE).

Groups	Relative weight of testes %	Relative weight of epididymes %	Testosterone level (ng/ml)
Control	0.62±0.500	0.18±0.012	2.1±0.30
G1	0.23±0.018***	0.112±0.018*	0.25±0.05***
G2	0.35±0.032***	0.142±0.100 *	0.21±0.01***

*** P<0.0001 , * P<0.01

3-Pathological findings:

3.1. Gross Examination

Testes from all treated animals appeared smaller than those of the control group (Table 2&3).

3.2. Histopathologic examination

Stained sections of testes in the control group showed more or less normal histological structure. Seminiferous tubules appeared as rounded or oval surrounded by a thin basal lamina. Primary and secondary spermatocytes, spermatids and spermatozoa were found. Interstitial tissues showed normal histology of blood vessels and leydig cells (Fig. 1). It was observed that control rats showed a normal histological appearance of ductus epididymes & interstitial tissue. The lumen of the epididymes contained numerous spermatozoa which were closely packed in the wide lumen of the ductus epididymes (Fig. 2)

Sections of testes and epidydimes in G1 group showed moderate degenerative and atrophic changes in both seminiferous tubules and epidydimal ducts compared with the control group, together with the presence of a number of abnormal tubules. Mild to moderate degeneration and necrosis of some of spermatogenic cells could be detected. Marked degenerative changes and necrosis were markedly shown in G2 group, associating with

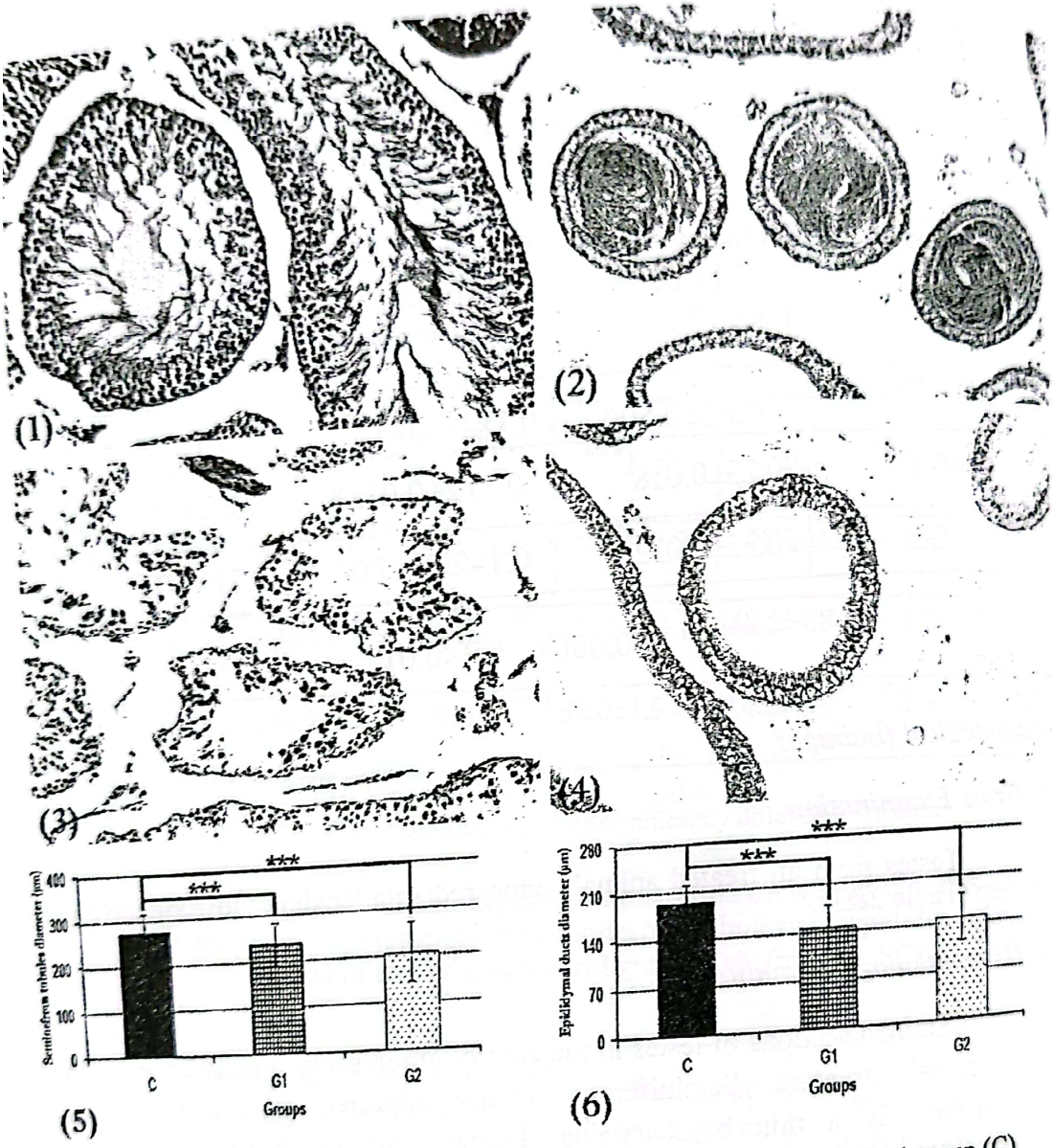

Fig. (1): Normal histological appearance of testes in rats of the control group (C) (HE,X200).

Fig. (2): Normal histological appearance of ductus epididymes in rats of the control group showing normal pseudostratified columnar epithelia and a lumen filled with mature sperms (HE, X200).

Fig. (3): Testes from rats of G2 showing different degrees of atrophic changes with distorsion of seminiferous tubules and disorganized germinal epithelia (HE, X200).

Fig. (4) Ductus epididymes in G2 showing prominence of intacellular vacoulation and absence of sperms in lumen (HE, X200).

Fig. (5): Mean diameter of seminiferous tubules (µm) in treated and control groups

Fig. (6): Mean diameter of epididymal (µm) in treated and control groups

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a decrease in spermatogenic cells and the presence of atrophic and abnormal tubules (Fig. 3). Number of these tubules was higher than that of the control group. The most conspicuous observation noted in epidydimes of this group (G2) was the appearance of small intracytoplasmic vacuolation, mild decrease in the diameter of ductus epididymes with irregular small lumen only in few ducts and absence of spermatozoa in the lumen (Fig. 4).

3.3. Morphometric analyses

Morphometric analyses of seminiferous tubules diameter (Table.2) reveled a significant decrease ($P<0.001$) in animals of treated group compared those in the control group (Fig. 5). Regarding epididymal duct diameters, similar finding could be observed ($P<0.001$) between treated and control groups (Fig. 6). No significant results between G1 and G2 were found.

Discussion

Certain medications possess the ability to damage cells producing sperm, lowering the sperm counts, with a toxic effect on the sperm motility. Tulathromycin is the first member of a new macrolide class, the triamildides, developed exclusively for veterinary use worldwide, and was demonstrated in reducing the incidence and severity of some respiratory diseases in swine (Nanjiani et al., 2005). The present study investigated the adverse effects of the repeated S/C injection of the therapeutic dose (2.5 mg/kg b.wt.) of tulathromycin on the fertility of male rats. Reported data suggested that fertility of rats was adversely affected by a repeated injection of tulathromycin at the used dose. The obtained findings revealed that tulathromycin administration in a dose of 2.5 mg/kg b.wt for the two groups induced a statistically significant decrease ($P<0.0001$) in sperm motility (18.3% and 30.6%) compared with the control group (86.4%). This is similar to that obtained by El-Sawy et al. (2013) who reported that tulathromycin induces a significant decrease in sperm motility (78%) after repeated administration of tulathromycin in a dose 10mg/kg b.wt. weekly for 8 successive weeks to male rats. Sperm motility have been reported to be reduced by some other antimicrobial agents such as amoxicillin, ceftazidin (Antohi et al., 2011), neomycin, gentamicin and streptomycin (Khaki et al., 2008). A decrease in sperm motility occurred as a result of increased the incidence of abnormal sperm and decreased live/dead ratio. The presence of abnormal sperm morphology might be due

to previously drug-induced effects including germ cell DNA damage, Y chromosomal abnormalities, defective acrosome formation, defective protein synthesis and somatic cell damage in testes (Narayana et al., 2002; Narayana et al., 2005). The increase in sperm abnormalities and decrease in sperm motility are associated with the decreased fertility (Narayana et al., 2002). Regarding sperm count, a significant reduction ($P<0.0001$) in sperm count for both experimental groups (0.2 and 0.19×106) as compared with the control group (1.04×106) has been found. This was quite similar to that mentioned by El-Sawy et al. (2013) who reported that tulathromycin induces a significant decrease in sperm cell count (0.35×106) after repeated administration of male rats by tulathromycin in a dose 10 mg/kg b.wt. weekly for 8 weeks. Meanwhile, the current findings agreed with those obtained by Khaki et al. (2008) who reported that neomycin had an adverse effect on spermatogenesis resulting in a marked reduction in sperm cell count. Moreover, the obtained data were in consistence with the earlier study reporting that neomycin have an adverse effect on the total sperm cell count in men (Itoh et al., 2006). Furthermore, results went parallel with that detected by Timmermans (1974) who found that the male fertility were negatively affected by antibiotics in the macrolide group (erythromycin, spiramycin and neomycin), and Meise et al. (1993) who exhibited that tylosin inhibits steroidogenesis in mice. The present study demonstrated that repeated subcutaneous administration of tulathromycin at a dose of 2.5 mg/kg b.wt in male rats induced a significant reduction in weights of testes and epididymes. This agreed with data recorded by El-Sawy et al. (2013) when administered tulathromycin once a week for 8 successive weeks in a dose of 10 mg/kg b.wt to male rats. Testosterone assay showed a significant decrease ($P<0.0001$) in the hormone levels in tulathromycin-treated groups compared with the control group. Results were similar to those observed with other antibiotics as gentamycin and ofloxacin (Khaki et al., 2009 b, Ghosh and Dasgupta, 1999).

Concerning histopathological findings, several morphometric literatures on rat testes have measured normal testicular parameters and their variations during the cycle of the seminiferous epithelium (Wing and Christensen, 1982) or under different experimental conditions (Mausle et al., 1982). So, the present study aimed to determine the testicular function not only by routine histopathologic examination, but also by estimating the seminiferous tubules and epididymal duct diameters. One of the most important histopathologic findings was the significant difference of diameters of seminiferous tubules and epididymal duct between treated and control groups which negatively pose on the spermatogenic cycle. Similar results were found using other types of antibiotic including aminoglycosides (Khaki et al., 2009a). Some studies show that ofloxacin at a dose of 72 mg/kg impaired the rat testicular histopathology (Abd-Allah et al., 2000). In the current investigation, declined spermatogonial cell number and consequently decrease in the number of spermatozoa in testes and epididymes as well as the significant difference of diameters of both seminefrous tubules and epididymal ducts was predominant, indicating that tulathromycin injection hindered the process of spermatogenesis, similar to other antibiotics including gentamicin, streptomycin and ofloxacin (Khaki et al., 2009a). Our findings agreed with those observed by El-Sawy et al. (2013) who reported that repeated administration of

tulathromycin for 8 weeks to male rats showed more or less pathological changes in testes (congested blood vessels and interstitial edema in the testes with normal histological appearance of spermatogenesis and presence of spermatozoa in the lumen of the seminiferous tubules). Pathological alterations were also compatible with those of CVMP (2002) who recorded that tulathromycin induced reproductive troubles in rats.

It could be concluded that subcutaneous administration of tulathromycin twice 15 days interval or once a week for three successive weeks in a therapeutic dose of 2.5 mg/kg b.wt. in male rats induced certain fertility troubles consisted of reduction of testes and epididymes weights, marked decreasing in seminiferous tubules and epididymal duct diameters, severe histopathologic changes in testes and epididymes, decrease testosterone level and changes in semen characters.

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تاثير المضاد الحيوى الماكروليدى "التليثروميسن "على الخصوبة فى ذكور الجرذان

عبير محمد راضى *نجلاء محمد عبد العظيم **الشيماء نبيل احمد ***و فاطمة حنفى سيد **
قسم الأدوية * وقسم الصحة و الرعاية والأمراض المشتركة **وقسم الباثولوجي
***كلية الطب البيطرى جامعة بنى سويف

يهدف هذا البحث إلى دراسة تأثير المضاد الحيوي الماكروليدى "التليثروميسن على الخصوبة . هذا وقد أجرى البحث على عدد ٣٠ جرز من ذكور الجرزان تم تقسيمهم إلى ثلاث مجموعات جرز المجموعة الأولى هى المجموعة الضابطة (تم حقنها مجموعات كل مجموعة مكونة من ١٠ ملى من محلول الملح الفسيولوجي تحت الجلد مرة كل أسبوع)والمجموعة الثانية حقنت بالتليثروميسن يوم . اما المجموعة ٠١ مجم لكل كجم من وزن الجرز تحت الجلد ثم حقنها بنفس الجرعة بعد ٢,٥بجرعة مجم لكل كجم من وزن الجرز تحت الجلد مرة كل اسبوع لمدة ٢,٥ الثالثة حقنت بالتليثروميسن بجرعة يوم وبعد ذلك تم ذبحها وتجميع عينات دم وحساب وزن ٥١ ثلاث أسابيع متتالية وتركت الجرزان لمدة الأعضاء التناسلية وقياس مستوى هرمون التيستيستيرون وتقييم صورة الحيوانات المنوية وكذلك الفحص الهستوباثولوجى للأعضاء التناسلية. وقدا سفرت النتائج فى هذا البحث ان حقن دواء التليثروميسن بجرعة مجم لكل كجم من وزن ٢,٥الجرز تحت الجلد احدث تغير ملحوظ فى صورة الحيوانات المنوية متمثلة فى قلة عدد وحركة الحيوانات المنوية وقلة مستوى هرمون التيستيستيرون فى المصل وكذلك وجود تغيرات باثولوجية فى أنسجة الخصية والبربخ. ومن هذة الدراسة لستخلص ان حقن الجرزان بالتليثروميسن بجرعة مجم لكل كجم من وزن ٢,٥ الجرز له تاثير سلبي على الخصوبة فى الجرذان.