International Journal of Pharmacology and Toxicology, 5 (2) (2017) 72-79

International Journal of Pharmacology and Toxicology

Website: www.sciencepubco.com/index.php/IJPT
doi: 10.14419/ijpt.v5i2.7778
Research paper

Changes in reproductive organs, semen characteristics and intra-testicular oxidative stress in adult male rats caused by azithromycin

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Abstract

This study aimed to evaluate the numerous azithromycin (as a member of macrolides) effects on the male reproductive organs, spermiogram, testicular oxidative stress markers of adults' male albino rats. Azithromycin was administered orally once daily to male rats (200-250 b.wt.) at a dose of 45 mg (therapeutic) or 90 mg/kg b.wt. (double-therapeutic) for three or six days and scarified at the first, thirty and sixty days after the last dose of administration.
A significant decrease as the index weight of the reproductive organs as well as sperm motility, livability and cell concentration, but sperm abnormalities increased at varying times post-treatment with azithromycin administration.
Testosterone hormone level did not vary significantly after azithromycin dosing for three days along the experimental period. However, it differed at the first day after the end of azithromycin dosing for six days.
The intra-testicular oxidative stress alteration mostly occurred at the thirty-day post-treatment in the three- and six-days protocols. In the three-days protocol, there was a significant decrease in malondialdehyde level and superoxide dismutase enzyme activity in a double-therapeutic group. In the six-days regimen, there was an increased activity of catalase enzyme, accompanied with a significant decrease in malondialdehyde levels as well as glutathione peroxidase enzymes.
Double therapeutic dose for six days' treatment was associated with vascular congestion and perivascular inflammatory cells and homogenous eosinophilic material infiltration into the stroma of testes. The lumen of seminiferous tubules and epididymis showed azoospermia.
From these results, it could be concluded that azithromycin administration has hazard effects on male adult's rats' fertility governed with the spermiogram, oxidative stress and the histopathological alternations during the post-treatment period.

Keywords: *Azithromycin; Histopathology; Spermiogram; Testicular Oxidative Stress; Testosterone; Rats.*

1. Introduction

Antibacterial agents are used for the treatment of many infections, cancer, protozoa and helminths. However, antimicrobial therapy has been shown to significantly affect semen parameters in human and animal models (Schlegel et al. 1991). Macrolides have the potential to serve a unique role in the management of inflammatory lung disorders (Martinez et al. 2008) and treatment of rhino sinusitis with or without lower respiratory tract disease due to their ability to modulate chronic inflammation (Cervin et al. 2009).
Azithromycin is a new 15-membered ring azalide antibiotic (Bright et al. 1998), improved the potency against gram-negative organisms (Retsema et al.1987), and excellent in vivo activity against localized infections because of its high sustained tissue levels produced by azithromycin (Girard et al. 1987&1990).
The objective of the current study was to evaluate the architecture various effects of azithromycin on male rats' reproductive organs histopathological structure or architecture and weights, spermiogram, testicular oxidative stress and testosterone level.

2. Material and methods

2.1. Drugs

Azithromycin, a subclass of macrolide antibacterial, is marketed by pharmaceutical company Pfizer as Zithromax®.
The diagnostic kits used for determining the values of catalase (Cat. No. CA 25 17), malondialdehyde (Cat. No. MD 25 29), superoxide dismutase (Cat. No. SD 25 21) and glutathione peroxide (Cat. No. GP 25 24) were obtained from Bio-diagnostic Co., Egypt. Other chemicals were purchased from EL-Gomhoria Co., Egypt.

2.2. Animals

Apparent healthy, sexually mature white albino (Rattus norvegicus. Bork) male Wistar rats (n=108, age 3 months old, weight 200-250 g) were obtained from the Animal House Department, El-Nile Co. for Pharmaceuticals and Chemical Industries, Cairo,

Egypt. Animals were housed in stainless steel cages (6 animals/ cage), were fed ad libitum commercial standard, rat pellets and access water were kept. Rats were acclimatized for two weeks prior to the experiments.

2.3. Experimental design

Azithromycin was administered once daily by oral route to male albino rats for three (Groups 1-3) or six (Groups 4-6) days. Male rats used in this study were designated into six groups as follows:
Group 1 (n=18) was used as a control group and received only normal saline.
Group 2 (n=18) received azithromycin at a therapeutic dose of 45 mg/kg b.wt.
Group 3 (n=18) received azithromycin at double-therapeutic dose of 90 mg/kg b.wt.
Group 4 (n=18) was used as a control group and received normal saline.
Group 5 (n=18) received azithromycin at therapeutic dose of 45 mg/ kg b.wt..
Group 6 (n=18) received azithromycin at the double-therapeutic dose of 90 mg/kg b.wt.
Both therapeutic and double-therapeutic doses of azithromycin were calculated according to (Paget & Barnes 1964).
The current investigation was extended for two months after the last repeated dose of administration to cover a complete spermatogenic cycle, which ranges from 48-56 days in rats (Clermont &Harvey 1965). Six rats were sacrificed from each group at the first, thirty and sixty days after the last dose of administrations.

2.4. Blood samples

Blood samples were collected via retro–orbital Plexus bleeding needle gauge, left to clot, centrifuged at 3000 rpm for 20 minutes and the separated sera were stored at -20°C until hormonal analysis.

2.5. Weight of reproductive organs

After blood sampling, animals were sacrificed, and the testes, epididymis, seminal vesicles and prostate were dissected out, grossly examined and weighed. The index weight (I.W.) of each organ was calculated (I.W. = organ weight (g) / body weight (g) × 100) according to (Matousek 1969).

2.6. Examination of epididymal sperm

The epididymal tail content of each rat was obtained after slicing in clean petri-dish contained 2 ml of warm normal saline (0.9%). The progressive motility, count of epididymal sperm and abnormalities were evaluated according to (Bearden & Fuquary 1980).

2.7. Testicular oxidative stress markers

Right testis was homogenized with phosphate buffer saline (pH 7.4) and centrifuged at 10000 rpm for 10 minutes at 4°C. The separated supernatant was stored at -20°C till being assayed for Catalase (CAT) enzyme according to (Aebi 1984), Malondialdehyde (MDA) according to (Ohkawa et al. 1979), Superoxide dismutase (SODs) enzyme according to (Nishikimi et al. 1972) and Glutathione peroxidase (GPx) enzyme according to (Paglia &Valentine 1967).

2.8. Testosterone assay

Serum testosterone was determined using a Competitive Enzyme Immunoassay kit (Cat. No.C29-852, Immunospec Corporation, Canoga Park) according to (Horton & Tait 1966).

2.9. Histopathological examinations:

Histopathological examination of the testes, epididymis and seminal vesicle was performed using standard laboratory techniques (Banchroft et al. 1996). Briefly, tissues were fixed in Bouin's solution, embedded in paraffin wax, sectioned at 5 µm thickness and stained with Mayer's hematoxylin and eosin (H&E).

2.10. Statistical analysis

Data were expressed as mean (± SEM) and statistically analyzed by One-Way ANOVA according to (Snedecor & Cochran 1982) using SPSS Ver. 16 Software (SPSS Inc., Chicago, USA) and differences between the means were examined by Duncan's multiple range tests (Duncan 1955). Data were statistically significant when p was < 0.05.

3. Results

3.1. Effect of azithromycin on male reproductive organs' weight

The effect of azithromycin dosage, at both therapeutic and double-therapeutic levels, for three and six days on adult male rats' organs index weight is demonstrated in table 1.
Oral administration of azithromycin for three days was found to be associated with a significant decrease in the testicular (at Day -1 and -30 post-treatment; in the therapeutic group), and epididymal (at Day -1 and -30; in the therapeutic group, at Day-60 post-treatment; in the double-therapeutic group). Seminal vesicle index weight increased at Day-1(in therapeutic group), before being decreased at Day-30 post treatment (in double-therapeutic group). Prostate gland index weight significantly decreased (at Day-1 only, in the therapeutic group) as compared with control.
Oral administration of azithromycin for six days was not associated with significant differences in the testicular index weight along the experimental period, but it affected epididymal, vesicular and prostatic index weight at the thirty-day post-treatment.

3.2. Effect of azithromycin on semen characteristics

Table (2) demonstrated effect of azithromycin–treated rats for three and six days on spermiogram. Azithromycin administration for three days showed a marked decrease in sperm motility (at a therapeutic dose; at the first day) and both sperm cell concentration (at both doses; at Day-30) but epididymal sperm tail abnormalities increased (at a therapeutic dose; at Day-30) while no significant difference in sperm viability.
Azithromycin treated rat for six days had a significant decrease in sperm motility (at the double therapeutic doses; at the first and sixty day) and sperm viability (at a therapeutic dose; at Day-30), a noticeable increase in an epididymal sperm head (at the therapeutic dose; at Day-1) as well as sperm tail (at both doses; at Day-30). This was concomitant with a significant reduction in sperm cell count (at both doses) at the first day post-treatment.

3.3. Effect of azithromycin on testosterone level

Testosterone hormone levels demonstrated non-significance differences after azithromycin treatment at both therapeutic and double-therapeutic doses for three days along the experimental period (Fig 1A).
On the other hand, there was a significant decrease in testosterone level at both doses at the first day post-treatment for six days (Fig 1B).

3.4. Effect of azithromycin on testicular

oxidative stress markers:

Effect of azithromycin on testicular oxidative stress markers is demonstrated in fig. 1C to J.

Azithromycin treatment for three days was accompanied with a significant decrease in malondialdehyde (Fig. 1E) and superoxide dismutase (Fig. 1G) enzyme activity at the thirty days; in double therapeutic group.

In 6-days treatment protocol, catalase enzyme activity significantly increased (Fig. 1D), while malondialdehyde (Fig. 1F) levels as well as glutathione peroxide activity (Fig. 1J) decreased during the period post-treatment.

3.5. Histopathological findings of azithromycin on reproductive organs

Figures (2) and (3) presented the histopathological changes in the azithromycin treated groups given for three and six days, respectively, by using therapeutic and double therapeutic doses.

At the sixty days, testes showed degenerative changes associated with blood vessel's congestion, perivascular inflammatory cells infiltration and homogenous eosinophilic material infiltration into the stroma. The lumen of seminiferous tubules as well as the epididymis showed absence of spermatozoa.

Mature male rats administered azithromycin for six days showed degeneration in some individual seminiferous tubules, congestion in the stromal blood vessels and edema of the connective tissue between the tubules at the first day, in addition to the appearance of giant cell spermatogonia in some of them at the thirty days. Azoospermia was noticed in the tubular lumen of the epididymis at Day-60: in an azithromycin treated groups. Seminal vesicles suffered from hyperplasia in the lining acinar epithelium in the therapeutic group at Day-1 in azithromycin-six-days treated groups.

Table 1: Effects of Azithromycin Administration on Male Rat Reproductive Organs

Organ	Time post-treatment (day)	Azithromycin for three days			Azithromycin for six days		
		Control	45 mg/kg b.wt.	90 mg/kg b.wt.	Control	45 mg/kg b.wt.	90 mg/kg b.wt.
		$\overline{X} \pm SE$	$\overline{X} \pm SE$	$\overline{X} \pm SE$	$\overline{X} \pm SE$	$\overline{X} \pm SE$	$\overline{X} \pm SE$
1. Testes	1	0.600 ± 0.027^{a}	0.490 ± 0.028^{b}	0.583 ± 0.026^{a}	0.606 ± 0.021^{A}	0.532 ± 0.024^{A}	0.586 ± 0.033^{A}
	30	0.515 ± 0.027^{a}	0.455 ± 0.028^{b}	0.486 ± 0.026^{ab}	0.585 ± 0.050^{A}	0.635 ± 0.034^{A}	0.572 ± 0.013^{A}
	60	0.511 ± 0.019^{a}	0.490 ± 0.017^{a}	0.488 ± 0.010^{a}	0.459 ± 0.012^{A}	0.467 ± 0.021^{A}	0.427 ± 0.012^{A}
2. Epididymis	1	0.201 ± 0.004^{a}	0.159 ± 0.009^{b}	0.181 ± 0.007^{a}	0.202 ± 0.014^{A}	0.144 ± 0.008^{B}	0.163 ± 0.004^{B}
	30	0.192 ± 0.004^{a}	0.169 ± 0.009^{b}	0.175 ± 0.007^{ab}	0.220 ± 0.017^{A}	0.219 ± 0.018^{A}	0.214 ± 0.009^{A}
	60	0.182 ± 0.011^{a}	0.183 ± 0.011^{a}	0.138 ± 0.009^{b}	0.168 ± 0.009^{A}	0.148 ± 0.017^{A}	0.162 ± 0.006^{A}
3. Seminal vesicle	1	0.234 ± 0.039^{b}	0.220 ± 0.043^{b}	0.498 ± 0.060^{a}	0.374 ± 0.055^{A}	0.242 ± 0.059^{A}	0.293 ± 0.051^{A}
	30	0.310 ± 0.039^{a}	0.255 ± 0.043^{ab}	0.244 ± 0.060^{b}	0.615 ± 0.051^{A}	0.564 ± 0.058^{AB}	0.467 ± 0.009^{B}
	60	0.390 ± 0.035^{a}	0.337 ± 0.026^{a}	0.389 ± 0.026^{a}	0.376 ± 0.030^{A}	0.342 ± 0.043^{A}	0.326 ± 0.031^{A}
4. Prostate gland	1	0.194 ± 0.032^{a}	0.083 ± 0.018^{b}	0.261 ± 0.020^{a}	0.203 ± 0.032^{A}	0.184 ± 0.039^{A}	0.188 ± 0.039^{A}
	30	0.198 ± 0.032^{a}	0.191 ± 0.018^{a}	0.176 ± 0.020^{a}	0.349 ± 0.029^{AB}	0.374 ± 0.026^{A}	0.289 ± 0.017^{B}
	60	0.278 ± 0.020^{a}	0.268 ± 0.005^{a}	0.246 ± 0.006^{a}	0.279 ± 0.017^{A}	0.247 ± 0.013^{A}	0.249 ± 0.018^{A}

Values (mean± S.E., n=6) with different superscript (lowercase or uppercase) letters within the same raw are significantly different at $p< 0.05$ (One-Way ANOVA with Duncan's multiple range test)

Table 2: Effects of Azithromycin Administration on Semen Characteristics

Organ	Item	Time post-treatment (day)	Azithromycin for three days			Azithromycin for six days		
			Control	45 mg/kg b.wt.	90 mg/kg b.wt.	Control	45 mg/kg b.wt.	90 mg/kg b.wt.
			$\overline{X} \pm SE$	$\overline{X} \pm SE$	$\overline{X} \pm SE$	$\overline{X} \pm SE$	$\overline{X} \pm SE$	$\overline{X} \pm SE$
1. Sperm motility (%)		1	60.83 ± 5.23^{a}	46.00 ± 4.30^{a}	50.00 ± 7.64^{a}	55.80 ± 5.97^{A}	30.00 ± 10.25^{B}	38.33 ± 6.91^{AB}
		30	75.00 ± 2.58^{a}	67.50 ± 3.10^{ab}	63.33 ± 3.57^{b}	79.17 ± 3.00^{A}	65.00 ± 5.77^{A}	72.50 ± 6.02^{A}
		60	77.50 ± 4.23^{a}	65.00 ± 4.08^{a}	65.83 ± 5.83^{a}	77.50 ± 1.70^{A}	70.83 ± 5.54^{AB}	61.67 ± 3.07^{B}
2.Sperm livability (%)		1	62.17 ± 5.31^{a}	51.00 ± 4.67^{a}	61.17 ± 4.90^{a}	50.17 ± 4.04^{A}	31.33 ± 14.15^{A}	42.33 ± 8.55^{A}
		30	67.67 ± 3.65^{a}	69.17 ± 4.20^{a}	65.33 ± 4.81^{a}	74.50 ± 2.09^{A}	61.67 ± 5.16^{B}	65.83 ± 3.47^{AB}
		60	75.83 ± 3.47^{a}	66.33 ± 4.51^{a}	71.00 ± 7.11^{a}	72.67 ± 4.21^{A}	68.67 ± 4.29^{A}	59.67 ± 4.85^{A}
3. Sperm conc. (10^{6}/gm of epididymis wt.)		1	117.00 ± 18.84^{a}	89.00 ± 15.92^{a}	82.67 ± 9.84^{a}	94.33 ± 13.40^{A}	40.17 ± 15.91^{B}	50.17 ± 21.64^{B}
		30	265.83 ± 20.91^{a}	190.00 ± 25.67^{b}	177.33 ± 13.17^{b}	148.17 ± 49.59^{A}	112.17 ± 30.24^{A}	124.83 ± 16.99^{A}
		60	157.33 ± 18.65^{a}	192.17 ± 23.72^{a}	143.83 ± 22.11^{a}	161.83 ± 11.47^{A}	146.83 ± 26.12^{A}	131.83 ± 19.39^{A}
4. Sperm Abnormalities (%)	Head ab.	1	2.17 ± 0.980^{a}	0.800 ± 0.800^{a}	4.67 ± 1.60^{a}	2.00 ± 0.894^{B}	0.330 ± 0.333^{B}	18.50 ± 5.60^{A}
		30	2.17 ± 0.703^{a}	1.00 ± 0.632^{a}	2.67 ± 0.955^{a}	3.00 ± 1.24^{A}	3.33 ± 1.15^{A}	1.33 ± 0.843^{A}
		60	0.000 ± 0.000^{a}	1.17 ± 0.749^{a}	0.670 ± 0.667^{a}	0.670 ± 0.670^{A}	0.00 ± 0.00^{A}	0.00 ± 0.00^{A}
	Tail ab.	1	36.50 ± 4.50^{a}	20.50 ± 2.36^{a}	38.00 ± 7.92^{a}	39.33 ± 5.13^{A}	31.17 ± 14.89^{A}	41.67 ± 10.17^{A}
		30	21.67 ± 1.23^{b}	37.50 ± 4.12^{a}	29.00 ± 5.13^{ab}	25.83 ± 2.83^{B}	37.50 ± 2.70^{A}	31.17 ± 3.97^{AB}
		60	33.00 ± 12.52^{a}	33.50 ± 5.73^{a}	34.67 ± 3.99^{a}	21.67 ± 3.85^{A}	20.33 ± 4.22^{A}	22.67 ± 3.96^{A}

Values (mean± S.E., n=6) with different superscript (lowercase or uppercase) letters within the same raw are significantly different at $p< 0.05$ (One-Way ANOVA with Duncan's multiple range test).

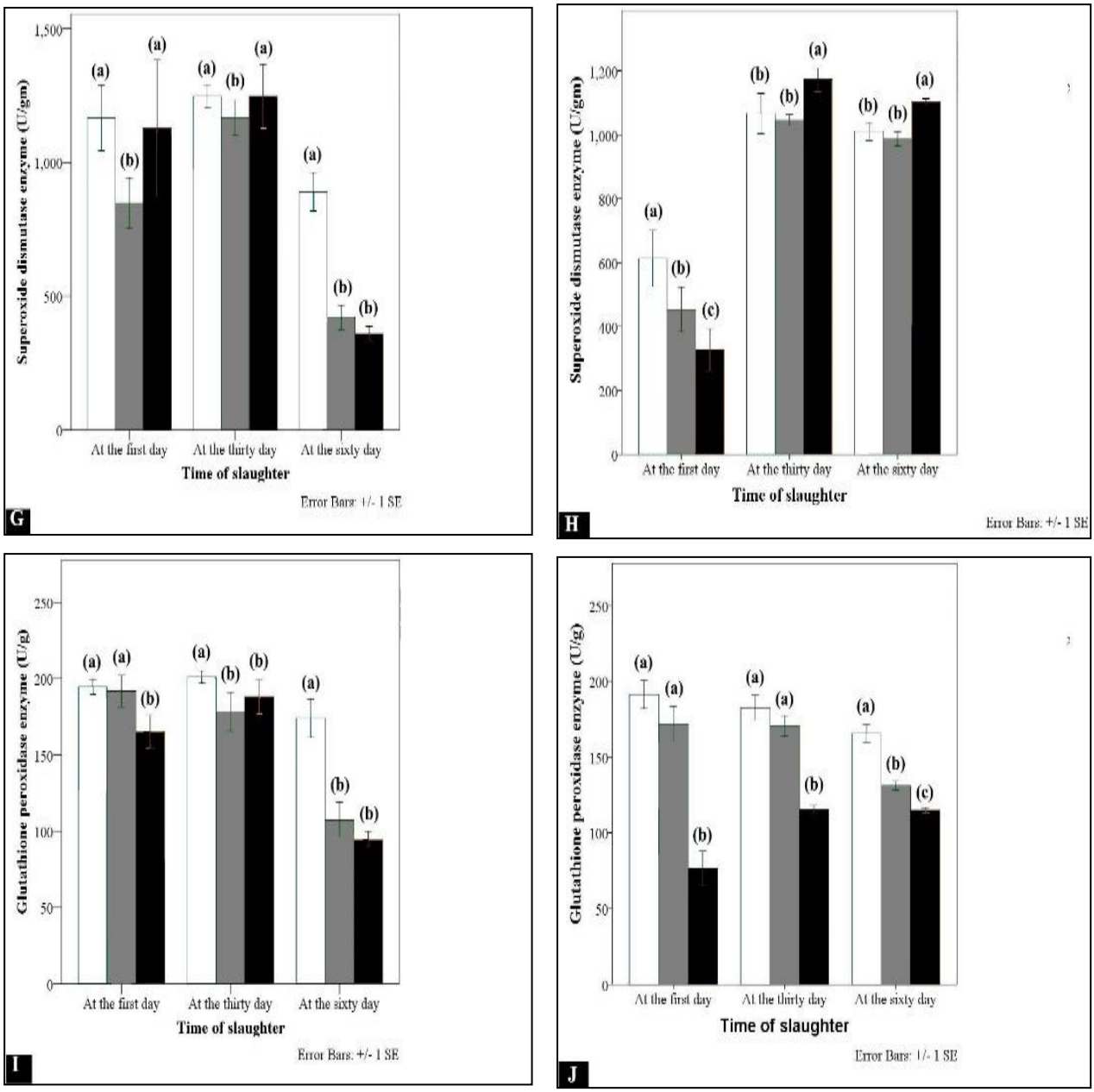

Fig. 1: Effect of Azithromycin on Testosterone Level (A&B), Catalase Enzyme (C&D) Malondialdehyde (E&F) Superoxide Dismutase Enzyme (G&H) and Glutathione Peroxidase Enzyme (I&J) in the Testis of Rats Administered Azithromycin in Control (□), Therapeutic (▣) and Double Therapeutic (■) Groups at the First, Thirty and Sixty Day after Last Repeated Oral Administration for Three and Six Days, Respectively.

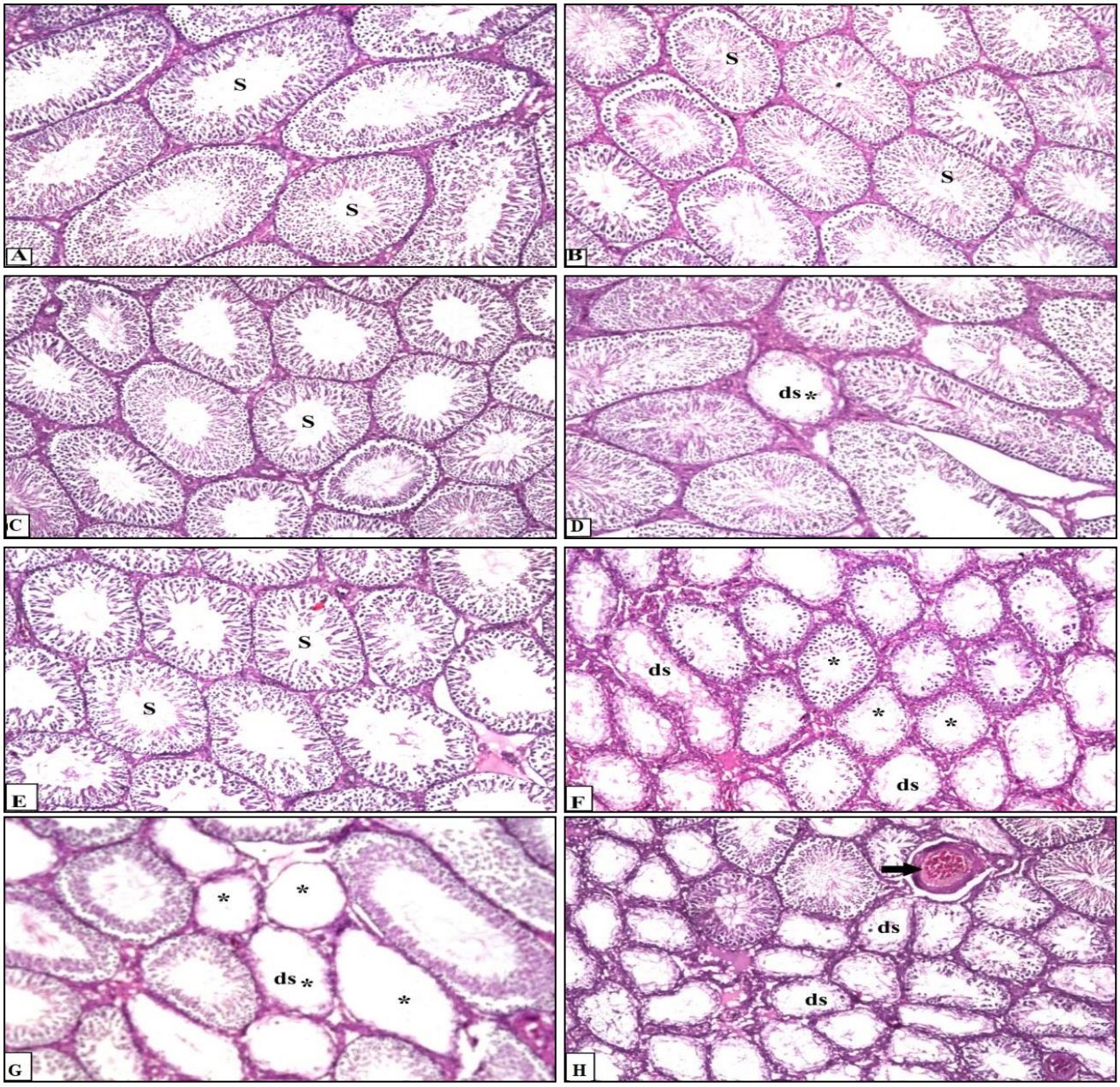

Fig. 2: A Representative Photomicrographs of Rat Testes at the First (A, B and C, D) and Sixty (E, F and G, H) Days after Daily Oral Administration of Therapeutic Dose (45 mg/Kg b.wt.) Double-Therapeutic Dose (90 mg/Kg b.wt.) For Three and Six Days of Treatment, Respectively. In 3-Days Protocol: Note the Pathological Alternation at Sixty Days (F) in A Double Therapeutic Group Characterized by Degeneration of the Seminiferous Tubules with the Absence of Spermatogenic Series (*). In 6-Days Protocol: Note the Pathological Changes in Therapeutic Group at Sixty Days Characterized by Degeneration and Absence of Spermatogenic Series in Some Seminiferous Tubules (*). Double Therapeutic Group Showed Degeneration with the Absence of Spermatogenic Series in Some Individual Seminiferous Tubules at the First (D) and Sixty (H) Days (*) In Association with Congestion in Interstitial Blood Vessels (Opened Arrow).

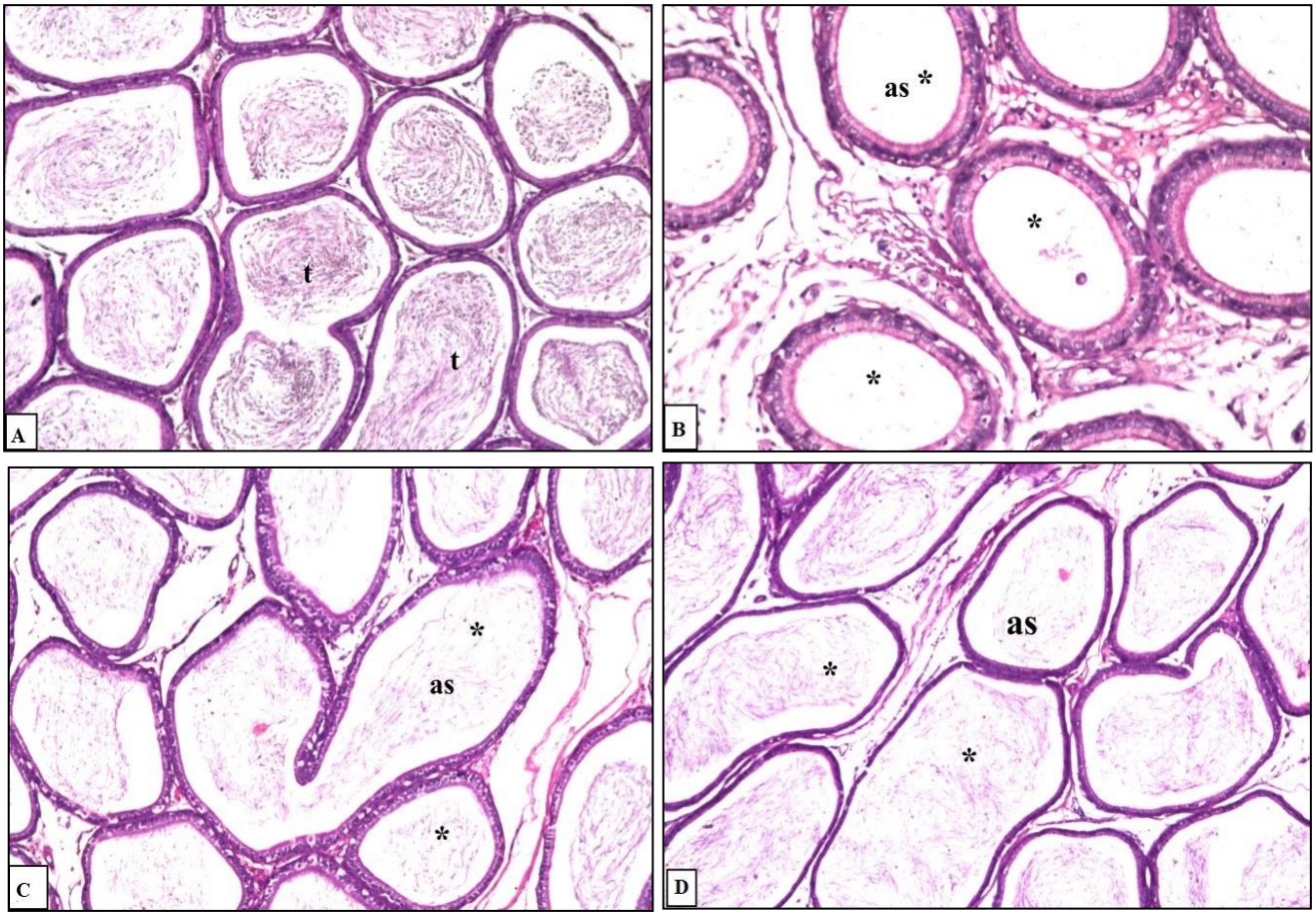

Fig. 3: Photomicrograph of Rat Epididymis at the Sixty (A, B and C, D) Days after Daily Oral Administration of Therapeutic Dose (45 mg/Kg b.wt.) Double-Therapeutic Dose (90 mg/Kg b.wt.) for Three and Six Days of Treatment, Respectively. Note That the Epididymis Showed Tubular Lumen was Emptied of Spermatozoa (As) in 3-Days (B) in 6-Days (C) Protocols (*).

4. Discussion

Macrolides are an old and well-established class of antimicrobial agents who account for 10 to 15% of the worldwide oral antibiotic market and considered to be one of the safest anti-infective groups in clinical use (Periti et al. 1993). However, the present study verified some adverse effect's azithromycin on male fertility exemplified with reproductive organs' weights, semen characteristics, testosterone level and testicular oxidative stress biomarkers.

In the current study, azithromycin administration negatively influenced gonadal and accessory sex glands index weight. The severity of testicular damage is related to the category of chemotherapeutic agent used, the dose and duration of therapy, and the developmental stage of the testis (Sikka 1999). Similarly, (El-Dakak 2015) demonstrated that the administration of azithromycin (20 mg/kg b.wt.) for three days caused a significant reduction in the relative weights of testis, epididymis and seminal vesicle. The reduction in male organs weights might be due to the marked parenchymal degenerative changed and/or atrophy of gonads and accessory sex organs verified in the histopathologic examination.

Moreover, the observed weight loss of the accessory sex organs might be due to high concentration of the bioactive macrolide antibiotic (Josamycin) in the prostate and seminal vesicles that affect the reproductive morpho-histological status (Schramm et al. 1988).

Side effects of drugs on male fertility occur more often than they are expected to. A transient or permanent inhibition of male fertility by drugs is possible, if one of the following functions was interfered: spermatogenesis, sperm maturation within the epididymis, sperm transport, sperm metabolism and motility, etc. (Schill & Przybilla 1985).

The lowered sperm viability and motility perhaps accused to the lowered spermatozoa metabolic activity and energy substrates (mainly fructose) in semen (El-Dakak 2015) in response to azithromycin administration. Moreover, macrolides (Erythromycin) have been to function by inhibiting protein synthesis and impair mitosis in rat spermatids, although the effects are reversible (Lastikka et al. 1976). Decreased sperm motility may be explained by the interference during the energy production process required for sperm viability and sperm motility (Folger et al. 1993).

Our results, concerned with sperm parameters, coincide with the results of (Bodetti et al. 2003) found a significant reduction of the motility of spermatozoa in erythromycin containing diluents. In an in-vitro study by (Hargreaves et al. 1998), it has been shown that erythromycin impaired sperm function at relatively high concentrations. (Berndtson & Foote 1976) It investigated the survival and fertility of antibiotic-treated bovine spermatozoa and observed that the high concentration of tylosin and erythromycin depressed its motility. Nevertheless, current data is not in agreement of the results of (Baker et al. 1984) declared that the erythromycin treatment has no significant effect on semen quality. (Schramm et al. 1988) It showed that Josamycin (0.5 mg/ml) did not impair, but even increased the motility of spermatozoa in-vitro. Improvement of sperm motility and activity in infertile patients was reported by (Al-Sultani 2000).

In the current study, while the testosterone hormone did not vary significantly after azithromycin dosing for three days, it differed at the first day after the end of azithromycin dosing for six days. The lowered hormone level might be due to Leydig's cell damage, which is responsible for testosterone production (Abd-Allah et al. 2000, Khaki et al. 2009).

These results disagreed with the findings reported by (El-Dakak 2015), who declared that the azithromycin administration for three days significantly decreased serum testosterone and interstitial stimulating hormones. The differences, perhaps due to the difference of the age and/or weight of the animals used (3 week and 45 g Vs. 3 months and 200-250 g, respectively).

In normal situation, the seminal plasma contains antioxidant mechanisms, which are likely to quench reactive oxygen species and protect spermatozoa against damage (Yadav et al. 2006).

Testicular oxidative stress marker's evaluation in the current study showed that the effect of azithromycin dosing mostly occurred at the thirty-day post-treatment in the three- and six-days protocols. There was a significant decrease in malondialdehyde and superoxide dismutase enzyme activity (double-therapeutic group) in a three-days protocol. In the meantime, malondialdehyde decrease was accompanied with an increased activity of catalase enzyme (therapeutic and double therapeutic group) and glutathione peroxidase (double therapeutic group) enzymes in a six-days protocol. Malondialdehyde (MDA) is formed during oxidative degeneration as a product of free oxygen radicals (Valenzuela 1990), which is accepted as an indicator of lipid peroxidation (Nielsen et al. 1997). Glutathione peroxidase catalyzes the reduction of hydrogen peroxide or lipid peroxides with reduced glutathione (Chan & Decker 1994). These results indicated that azithromycin did not cause lipid peroxidation in the testes at three-days treatment protocol, but this was emphasized with six days' treatment. The current results are in agreement with (El-Dakak 2015), who treated rats orally with azithromycin and found decreased activities of antioxidant enzymes superoxide dismutase, catalase and glutathione peroxide in the testis.

The current study illustrated a significant histopathological alternation in reproductive organs of 3-days azithromycin-treated rates in the testes at the sixty-day post-treatment in association with double-therapeutic dosing. In contrary, six days' treatment protocol induced degeneration in the gonads at the sixty days in therapeutic group, and along the studied period in the double therapeutic group. Altered seminal vesicles were evident in rats given azithromycin for six days at therapeutic doses. These findings were in agreement with those recorded by (El-Dakak 2015), who demonstrated that administration of azithromycin caused severe histopathologic lesions such as vacuolations and degeneration of spermatogonial cells lining the seminiferous tubules. (Olayinka & Ore 2014) It accused these disorders to the formation of highly reactive radicals that disrupted the normal cellular functioning of the organs. Since the oxidative stress-status induces cellular and DNA damage (Tramer et al. 1998), it is possible that the cell death and consequent tubular atrophy, at least in a few tubules, would have been the response of the seminiferous epithelium to the altered biochemical milieu in the testis (Olayinka & Ore 2014).

5. Conclusion

The present study spotted the light on the potential risk of using azithromycin (a member of the macrolides group) on reproductive health statuses. Azithromycin represents hazardous effects on the male fertility through conflicting with testosterone hormone secretion, normal spermiogram, intra-testicular oxidative stress mechanism. This was complemented by the gross weight as well as histopathological alternation of the reproductive organs. Taken together, the use of azithromycin antibacterial should be kept above the minimum, with caution on the double therapeutic dose or prolonged time of administration.

Acknowledgement

The author would like to thank the Prof. Dr. Adel Bakeer Kholoussy, Pathology Department, Faculty of Veterinary Medicine, Cairo University, for his valuable help in the histopathological examination. Also, special thanks to the members of the Center of Excellence in Scientific Research (CESR), Faculty of Veterinary Medicine, Benha University, for their help in laboratory assays done in this study.

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