Proteção Efetiva de Vitamina E Contra os Efeitos Induzidos por Moxifloxacino em Ratos

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Abstract | Nossa investigação foi realizada para avaliar o efeito protetor de vitamina E contra os efeitos indutivos do moxifloxacino em ratos. Um total de 80 ratos albino machos adultos foram distribuídos em quatro grupos iguais. O primeiro grupo representou o grupo controle e recebeu solução salina fisiológica. O segundo e terceiro grupos foram recebidos oralmente vitamina E (18 mg/kg BW) e moxifloxacino (7.2 mg/kg BW), respectivamente, durante 21 dias consecutivos. O quarto grupo recebeu Vit E concurrentemente com moxifloxacino por 21 dias consecutivos. A administração de moxifloxacino em ratos resultou em aumento significativo nas atividades de ALT (Alanina aminotransferase), AST (Aspartato aminotransferase), ALP (Fosfatase Alkalina) e diminuição significativa dos níveis de proteínas totais e albumina, além de uma elevação nas concentrações de creatinina e ureia ao longo do período experimental em comparação com o grupo controle. Além disso, um efeito significativo de diminuição nas atividades de catalase (CAT), superóxido dismutase (SOD) e glutatiónio peroxidase (GPx), bem como uma elevação significativa na concentração de malondialdeído (MDA) foram registrados no grupo tratado com moxifloxacino quando comparado com o grupo controle. A co-administração de moxifloxacino com Vit E por 21 dias consecutivos resultou em uma redução significativa nas atividades de enzimas hepáticas, creatinina e ureia, enquanto as proteínas totais, albumina e globulina viraram para os níveis normais, além de um aumento de CAT, SOD e GPx com uma redução significativa na concentração de MDA quando comparado com o grupo tratado com moxifloxacino. Os resultados revelaram que Vit E poderia proteger contra os efeitos indutivos do moxifloxacino. Portanto, Vitamina E deve ser usada com moxifloxacino para reduzir seus efeitos adversos.

Chave Palavras | Atividade antioxidante, Funções de Fígado e Núcleo de Cais, Moxifloxacino, Vitamina E

INTRODUÇÃO

O fluoroquinolona antimicrobianas é utilizada no tratamento de uma variedade de doenças bacterianas; no entanto, sua terapêutica tem sido associada com efeitos tóxicos variados (Leone et al., 2003; Owens and Ambrose, 2005; Thompson, 2007; de Guidi, 2011). O mecanismo de ação de fluoroquinolonas envolve a inibição de gírase de DNA (DNA gyrase) (topoisomerase II) e (topoisomerase IV), enzimas envolvidas na replicação de DNA bacteriano, transcrição, reparo e recombinação (Thompson, 2007; Sinbad et al., 2019). Moxifloxacino é um quarto geração de fluoroquinolona antimicrobiana (anteriormente conhecido como BAY 12-8039) e é anunciado mundialmente sob a marca comercial avelox. Moxifloxacino é ativo contra ambos os Gram-positivos e Gram-negativos. O moxifloxacino é um novo agente que pode ter se juntado a outros agentes antituberculóticos ao avaliar o efeito de moxifloxacino na doença tuberculosa (Minov et al., 2018).

Fluoroquinolonas (Moxifloxacino e Ciprofloxacino) causam artrite em adolescentes e estão relacionadas com problemas musculosqueleticos reversíveis nos jovens.
and adults. Other unfriendly impacts include deleterious effects on sensory system, liver and kidney functions, etc., (Committee of infectious diseases, 2006).

Vitamin E is a term corresponding to a small group of tocopherols of which α-tocopherol is the most bioactive, being also considered to be the most potent antioxidant of the lipid soluble form, responsible for the protection of membrane polyunsaturated fatty acid against lipid peroxidation (Carletti et al., 2007; Eraslan et al., 2007). Vitamin E primarily induces an antioxidant effect and is known to be the compound with the highest biological activity. Vitamin E acts as a free radical scavenger in the prevention of diseases and thereby inhibits lipid peroxidation (El-Demerdash, 2004).

The present study was designed to assess the (i) adverse effects of moxifloxacin and (ii) protective effect of vitamin E as antioxidants through investigation of some liver and kidney function tests beside oxidant/antioxidant status and histopathological changes in liver and kidney.

MATERIALS AND METHODS

DRUGS
Moxifloxacin tablet (avelox®, 400 mg), was obtained from Future pharmaceutical industries. Human therapeutic dose of moxifloxacin converted to rat dose according to (Paget and Barnes, 1964). Vitamin E (capsule, 1000 mg) was purchased from PHARCO pharmaceutical industries CO., Alex, Egypt.) and was dissolved in corn oil.

ANIMALS
Eighty adult male albino rats weighed 150 to 170g were used in the study. They were purchased from laboratory animal farm, Faculty of Veterinary Medicine, Zagazig University. They were housed in polypropylene cages in a temperature and humidity-controlled room. All animals were allowed access to food, water ad libitum. Animal housing and care and the experimental protocols were conducted as stipulated in the Guide for the Care and Use of Laboratory Animals by the National Institutes of Health (NIH) and as approved by the local authorities of Zagazig University, Zagazig, Egypt. All efforts were made to minimize animal suffering. They were kept for two weeks before being used in the study.

EXPERIMENTAL DESIGN
Before dose administration, the body weight of each animal was determined and the dose was calculated according to the body weight. Rats were classified into 4 groups each contain 20 rats, 1st group (control), rats in this group were not medicated and received normal saline. Second group (Vit. E), rats in this group received repeated oral doses of vitamin E (100 mg/kg BW once daily) for 21 successive days (El Maghraby and Taha, 2012) as a standard antioxidant. Third group (Moxifloxacin), rats received a repeated oral dose of moxifloxacin (7.2 mg/kg BW once daily) for successive 21 days (Pardillo et al., 2008). Fourth group (Moxifloxacin - Vitamin E) rats in this group received repeated oral doses of Moxifloxacin (7.2 mg/kg BW) concurrently Vitamin E (100 mg/kg BW) once daily for 21 days.

PREPARATION OF SERUM SAMPLE AND TISSUE SAMPLE
Rats were sacrificed and blood samples were collected in a sterile Wassermann tube without anticoagulant from 5 rats/group on the 1st, 7th, 14th and 21st days post treatment and allowed to clot for 30 minutes and serum was separated by centrifugation at 3000 rpm for 15 minutes, the top yellow layers of serum were pipette off without distributing the white buffy layer. Serum was stored at -20°C in Eppendorf tubes till the determination of serum biochemical analysis. Liver and kidney of each rat were collected on 7th and 14th days post treatment. They were kept in 10% neutral-buffered formalin for histopathological examination.

DETERMINATION OF LIVER AND KIDNEY FUNCTION
The preserved serum used for determination of the activities of alanine aminotransferase (ALT), and aspartate aminotransferase (AST) (Tietz, 1976), alkaline phosphatase (ALP) (Belfield and Goldberg, 1971), creatinine (Henry et al., 1974), urea (Vassault et al., 1986), total protein and albumin (Gassbaro et al., 1972). Serum globulin was calculated by subtraction of the obtained albumin level from total protein level.

DETERMINATION OF OXIDANT/ANTIOXIDANT STATUS
The activities of catalase (CAT), superoxide dismutase (SOD) and glutathione peroxidase (GPx) and malondialdehyde (MDA) concentration were determined according to Áebi (1984); Nishikimi et al. (1972) and Pagila and Valentine (1967), respectively.

HEPATIC AND RENAL HISTOPATHOLOGICAL EVALUATION
Liver and kidney tissues were kept in 10% neutral-buffered formalin for 24 h at that point tissue handling and paraffin blocks preparation were done (Suvarna et al., 2013).

STATISTICAL ANALYSIS
The obtained data were statistically was analyzed using one-way analysis of variance (ANOVA) according to Tamhane and Dunlop (2000) followed by Duncan’s multiple range post hoc test for pairwise comparisons. Differences were considered significant at $p < 0.05$.

RESULTS AND DISCUSSION
It was clearly evident from Table 1 that the administration
of moxifloxacin for 21 successive days to albino rats resulting in a significant increase (p<0.05) in the activities of ALT, AST, ALP on 1st, 7th, 14th and 21st day post treatment besides significant increase (p<0.05) in the levels of total serum protein and on 1st, 7th, and 14th day post treatment compared with control group. Co-administration of moxifloxacin and Vit. E for 21 successive days to albino rats resulting in a significant decrease (p<0.05) in the activities of ALT, AST, ALP after 1st, 7th, 14th and 21st day post treatment while the levels of total serum protein and albumin were significantly (p<0.05) increased on the 14th day post treatment compared with moxifloxacin group.

Table 2 illustrated that the administration of moxifloxacin to albino rats resulting a significant (p<0.05) increase in creatinine and urea levels when compared with the control

| Days          | Groups          | Creatinine (mg/dl) | Urea (mg/dl) | CAT** (U/L) | SOD** (U/ml) | GPx# | MDA## (nmol/ml) |
|---------------|-----------------|-------------------|-------------|-------------|-------------|------|---------------|
| 1st Day       | Control         | 0.706 ± 0.008      | 23.47 ± 1.23 | 241.39 ± 3.49 | 22.54 ± 1.69 | 112.93 ± 1.92 | 7.04 ± 0.14  |
|               | Vitamin E       | 0.706 ± 0.044      | 23.94 ± 1.60 | 247.85 ± 2.12 | 23.90 ± 2.05 | 111.40 ± 3.30 | 6.75 ± 0.50   |
|               | Moxifloxacin    | 1.52 ± 0.040       | 58.78 ± 2.35 | 184.46 ± 2.85 | 9.21 ± 0.49 | 85.08 ± 2.49  | 17.28 ± 0.50  |
|               | Moxifloxacin+Vit.E | 1.25 ± 0.065   | 53.98 ± 3.04 | 200.91 ± 2.34 | 14.11 ± 0.73 | 97.73 ± 1.40  | 11.74 ± 0.94  |
| 7th Day       | Control         | 0.760 ± 0.015      | 24.63 ± 1.35 | 233.77 ± 2.47 | 20.91 ± 1.19 | 116.91 ± 0.96 | 7.11 ± 0.52   |
|               | Vitamin E       | 0.743 ± 0.033      | 23.61 ± 1.00 | 235.01 ± 4.91 | 22.58 ± 0.85 | 113.51 ± 1.45 | 7.52 ± 0.34   |
|               | Moxifloxacin    | 1.180 ± 0.064      | 48.12 ± 2.50 | 193.44 ± 1.91 | 13.88 ± 0.93 | 92.62 ± 2.69  | 11.82 ± 0.64  |
|               | Moxifloxacin+Vit.E | 0.980 ± 0.025   | 44.11 ± 2.51 | 208.99 ± 5.29 | 19.39 ± 0.57 | 108.13 ± 4.52 | 8.49 ± 0.29   |
| 14th Day      | Control         | 0.746 ± 0.018      | 24.39 ± 0.55 | 228.78 ± 8.22 | 20.04 ± 0.62 | 116.04 ± 3.99 | 7.05 ± 0.53   |
|               | Vitamin E       | 0.760 ± 0.020      | 23.47 ± 0.60 | 224.15 ± 8.02 | 21.59 ± 0.99 | 111.25 ± 5.83 | 7.64 ± 0.14   |
|               | Moxifloxacin    | 0.980 ± 0.073      | 42.90 ± 1.14 | 208.50 ± 1.36 | 17.68 ± 0.74 | 99.78 ± 2.43  | 7.78 ± 0.54   |
|               | Moxifloxacin+Vit.E | 0.883 ± 0.042   | 37.26 ± 3.72 | 221.06 ± 3.83 | 20.88 ± 0.69 | 114.72 ± 2.57 | 7.82 ± 0.32   |
| 21st Day      | Control         | 0.786 ± 0.014      | 22.11 ± 0.85 | 229.69 ± 5.25 | 21.58 ± 0.92 | 118.48 ± 2.75 | 7.43 ± 0.07   |
|               | Vitamin E       | 0.783 ± 0.024      | 22.84 ± 0.67 | 227.58 ± 0.06 | 21.78 ± 0.40 | 114.60 ± 4.82 | 7.66 ± 0.16   |
|               | Moxifloxacin    | 0.863 ± 0.057      | 35.72 ± 2.14 | 216.04 ± 0.80 | 20.26 ± 0.73 | 110.39 ± 2.96 | 7.35 ± 2.29   |
|               | Moxifloxacin+Vit.E | 0.793 ± 0.031   | 24.18 ± 3.72 | 228.56 ± 2.89 | 22.95 ± 0.18 | 119.00 ± 3.97 | 7.72 ± 0.30   |

Means within the same column (at the same time point) carrying different superscripts are significantly different at p<0.05. * CAT: catalase; ** SOD: superoxide dismutase; # GPx: glutathione peroxidase; ## MDA: malondialdehyde.
group on 1st, 7th, 14th, and 21st days post treatment. Co-administration of moxifloxacin and Vit E for 21 successive days to albino rats resulting in significant (p<0.05) decrease in serum creatinine and serum urea level on 1st, 7th, 14th and 21st days post treatment when compared with moxifloxacin only group.

It was clearly evident from Table 2 that the administration of moxifloxacin in therapeutic dose for 21 successive days in albino rats resulted in a significant (p<0.05) decrease in CAT, SOD and GPx on 1st, 7th, 14th, and 21st days post treatment when compared with the control group. The co-administration of moxifloxacin with Vit E for 21 successive days to albino rats resulting in significant (p<0.05) increase in CAT, SOD and GPx on 1st, 7th, 14th and 21st days post treatment when compared with moxifloxacin group. The administration of moxifloxacin for 21 successive days to albino rats resulted in a significant (p<0.05) increase in MDA concentration on 1st and 7th, 14th days post treatment when compared with the control group. While, co-administration of moxifloxacin and Vit E combination for 21 successive days to albino rats resulting in return to nearly normal concentration of MDA when compared with moxifloxacin group.

**Histopathological Results**

On the 14th days post treatment Examined sections from liver showed normal hepatic parenchyma with preserved hepatic lobulation. Sections from kidney revealed apparently normal renal structures (Figure 1). Liver sections of rats received vitamin E, showed apparently normal hepatic parenchyma with preserved lobular pattern, cord arrangement, vascular tree, sinusoids, kupffur cells and portal area structures. Kidney sections showed normal nephron units with preserved renal papillae, renal pelvis and stroma (Figure 2). Liver sections of moxifloxacin treated rats showed multifocal hepatic necrosis of variable sizes, partially replaced by macrophages occasionally with giant cells formation. The hepatic blood vessels were moderately congested and the bile ducts were proliferated with characteristic portal round cells aggregation and portal fibrosis (Figure 3). Examined sections from kidney showed cystic dilatation of few tubules in the medulla and cortex. The renal pelvis revealed focal sloughing and hyperplastic changes in the transitional epithelium. Focal interstitial and perivascular aggregation of round cells and eosinophils were observed. The renal blood vessels were mildly congested with mild perivascular edema (Figure 4). Liver sections of Moxifloxacin + Vit E treated rats showed normal hepatic parenchyma with residual portal biliary proliferation and fibrosis. Minute focal hepatic necrotic areas partially replaced by round cells were also seen. The hepatic blood vessels were mildly congested and the kupffur cells were prominently enlarged and focally proliferated (Figure 5). Renal Sections of with moxifloxacin + Vit E treated rats showed apparently normal nephron units with mild degenerative changes in some tubular epithelium (cloudy swelling and hydropic degeneration) and cystic dilatation of a few tubules in the cortex and medulla (Figure 6).

**Figure 1:** Photomicrograph of control (untreated) group of liver (A and B) showing normal hepatic parenchyma. Kidney (C and D) showing normal renal parenchyma. H&E X 100 (A, C), H&E X 400 (B, D).

**Figure 2:** Photomicrograph of vitamin E treated group of liver (A and B) showing normal hepatic parenchyma with preserved lobular pattern, cord arrangement, vascular tree, sinusoids, kupffur cells and portal area structures. Examined sections from Kidney (C and D) showed normal nephron units with preserved renal papillae, renal pelvis and stroma. H&E X 100 (A, C), H&E X 400 (B, D).
Figure 3: Photomicrograph of Liver of moxifloxacin-treated rats showing multifocal hepatic necrosis of variable sizes (circle), partially replaced by macrophages (arrow) and giant cells (curved arrow). Bile ducts proliferated with characteristic portal round cells aggregation (arrow head) and fibrosis (star) are seen. Some sections showing Centrilobular degenerative changes in some hepatic lobules and hyper trophyed kupffur cells. H&E X 100 (A, C), 400 (B, D).

Figure 4: Photomicrograph of kidney of moxifloxacin-treated rats showing focal sloughing (circle) and hyperplastic changes (black star) in the transitional epithelium of pelvis, focal interstitial and perivascular aggregation of round cells (yellow arrow) and eosinophils (red arrow). Some of the cortical and medullary tubules showed cyst changes. The renal blood vessels showed congestion with mild perivascular edema. A few renal tubules shows degenerative and necrotic changes. H&E X 100(A, C), 400 (B, D).

Activities of ALT, AST, and ALP after one day post-administration when compared with control group. The same results were recorded by Ore and Olayinka (2015) who found that an elevation in the activities of serum ALT, AST and ALP beside a significant rise in serum urea in Sprague-Dawley rats of both sexes received oral dose of 8 mg/kg b.w. moxifloxacin for 7 successive days. Co-administration of moxifloxacin and Vit E to mature male rats induce significant decrease in the activities of AST, ALT and ALP in its therapeutic dose at 1st, 7th, 14th and 21st days compared with group III which treated with moxifloxacin only.

Figure 5: Photomicrograph of moxifloxacin + Vit E treated group, liver showing apparently normal hepatic parenchyma with residual portal biliary proliferation (curved arrow), minute focal hepatic necrotic areas (black star) partially replaced by round cells (open arrow). The hepatic blood vessels showing mild congestion (yellow star) in addition to hypertrophied kupffur cells (arrow head). H&E X 100 (A, C), H&E X 400 (B, D).

Figure 6: Photomicrograph of kidney of moxifloxacin + Vit E treated group, (A and B) showing apparently normal nephron units with mild degenerative changes in some tubular epithelium (curved arrow) and cyst dilatation of some renal tubules (star). H&E X 100 (A), H&E X 400 (B).

The obtained results in this study revealed that oral administration of moxifloxacin for 21 successive days to
mature male rats resulted in a marked decrease of total serum protein, and albumin all over the experimental periods when compared with normal control group. The obtained results were parallel to those obtained by Sadariya et al. (2010) who recorded a significant reduction in serum total protein and serum albumin in male and female wistar rats injected intramuscularly with moxifloxacin at doses of 5 mg/kg repeated at 24 hours interval for 14 days. Co-administration of moxifloxacin + Vit E on 1st, 7th, 14th and 21st days to mature male rats induces significant increase in total serum proteins and serum albumin when compared with group III which received moxifloxacin only.

The administration of moxifloxacin to albino rats resulted in a significant increase in serum creatinine and urea levels when compared with the control group on 1st, 7th, 14th, and 21st days post treatment. Also, Öre and Olayinka (2015) who recorded an elevation in serum creatinine and urea in Wistar rats which received oral dose of 1 ml each of moxifloxacin equivalent to 4 mg/kg BW, 8 mg/kg BW, and 16 mg/kg BW, for 7 days.

Antioxidants are substances that when show at low concentrations contrasted to those of an oxidizable substrate (e.g. proteins, lipids, carbohydrates and nucleic acids) altogether delays or suppress oxidation of that substrate (Halliwell et al., 1996). Reactive oxygen species (ROS) are constantly created as a metabolic item by basically all tissues in moderately small amounts. Every mammalian cells contain various distinctive enzymatic and non-enzymatic antioxidants that serve to counteract or limit oxidative tissue damage. The principal line of safeguard against oxidative insult is the antioxidant enzymes superoxide dismutase, catalase, and glutathione peroxidase. The non-enzymatic guards incorporate assortment of low molecular weight scavenger, and reductants, and also a few different iron chelators (Halliwell et al., 1994).

An extraordinary supporter of non-enzymatic assurance against lipid peroxidation is Vitamin E (Vit. E), a known free radical scavenger. Vit. E as a lipid solvent, chain-breaking antioxidant plays a critical defensive part against oxidative stress and prevents the creation of lipid peroxides by searching free radicals in biological membranes (Ellis et al., 2017).

It has been suggested that free radicals created after medication by fluoroquinolones, assume a critical part in these antibiotics’ toxicity (Thompson, 2007). Numerous antioxidant enzymes, including SOD, CAT, and glutathione GPx, are viable in evacuating destructive ROS. Lacking action of intracellular antioxidant enzymes can make damage to cell structures. Whenever unbalanced, it might prompt oxidation of polyunsaturated fatty acids in lipids, amino acids in proteins, and obliterate DNA (Mari et al., 2010; Beberok et al., 2015). In this study, it has been observed that moxifloxacin causes critical decrease in the activities of the antioxidant enzymes: SOD, CAT, and GPx in melanocytes. SOD ensures cells by dismutating superoxide anion into the proradical hydrogen peroxide, which thusly is inactivated to water and oxygen by catalase or other H₂O₂ –evacuating enzymes such as glutathione peroxidase (Finaud et al., 2006).

Vitamin E is a lipid-solvent vitamin, of which α-tocopherol is the most strong. Vitamin E acts as an antioxidant in cells, intruding on the spread of lipid peroxidation in the plasma membrane and in this way safeguarding membrane integrity (Chow, 1991). Very responsive molecules called free radicals can cause tissue damage by responding with polyunsaturated fatty acids in cell membranes, the degree of tissue damage is the consequence of the harmony between the free radicals created and the antioxidant protective defense system (Lawrence and Adriam, 1987). Vitamin E is the best lipid-dissolvable, chain-breaking antioxidant, shielding cell membrane from peroxidative damage. Free radicals have been involved in the improvement of degenerative sicknesses and conditions (Lester, 1991). When the antioxidant defense in the human body becomes overwhelmed, oxidative stress to the parts frequently happens, initiating inflammatory, adaptive, and reparative procedures (Borut and Rok, 2014). As of late, Vit E is being widely examined because of its activity against oxidative stress. Its defensive part on biological membranes is identified with its impact on delaying the side effects of aging (Enesco et al., 1980). The in vivo function of Vit E as an antioxidant has not yet been completely studied (Kumar and Adarad, 1988). Ongoing investigations have uncovered that Vit. E has an antioxidative activity in shielding cells from damage by highly responsive superoxide free radicals (Mokhtari et al., 2017).

Vitamin E normalized levels of catalase, superoxide dismutase, glutathione peroxidase, malondialdehyde and enhanced histopathological changes occur in liver and kidney induced by receiving of moxifloxacin. The possible pathway can be clarified through structure of Vitamin E, the side chain in the 2-position encourages the consolidation and maintenance of Vit. E in bio films, with the goal that the 6-position is responsible for rummaging free radicals and ending lipid peroxidation. Antioxidant impact of vitamin E is shown through insurance of polyunsaturated fatty acids from oxidation by reactive oxygen species making adjustment of membrane and breaking of antioxidant chains that counteract responsive oxygen species harm to membrane.

In this study Vit. E utilized in a dose of (100 mg/kg, orally once daily) to clarify the hepatic-nephroprotective effect on rats, we find a critical rise in the activities of anti-oxidative...
stress enzymes (SOD, CAT, GPx) besides a decrease in MDA activity.

CONCLUSIONS AND RECOMMENDATIONS

Our results revealed that moxifloxacin administration induced alterations in liver and kidney functions and has an oxidative stress effect and could cause some histopathological changes in liver and kidney cells of rats. The combination of Vit E and moxifloxacin declared better results compared to Moxifloxacin alone. Therefore, Vitamin E has a protective effect against moxifloxacin’s side effects.

AUTHOR’S CONTRIBUTION

All authors contributed equally to this work.

CONFLICT OF INTEREST

The authors have declared no conflict of interest.

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