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RESEARCH ARTICLE

The Possible Effects of Montelukast against Doxorubicin- Induced Nephrotoxicity in Rabbits

Haider F. Al-Saedi [1] , Adeeb A. Al-Zubaidy [1], Yaurb I. Khattab[2]

1 Department of Pharmacology, College of Medicine, Al-Nahrain University.
2 Department of Pathology, College of Medicine, Al-Nahrain University.

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***Corresponding Author**

Haider F. Al-Saedi

Abstract

Background
Doxorubicin is a potent chemotherapy agent used to treat a broad spectrum of malignancies, but it has a significant nephrotoxicity which associated with increase generation of active metabolite and reactive oxygen radicals that damaged cells membranes through lipid peroxidation of kidney with decreased levels of antioxidants compounds.
Objective: the present study aimed to evaluate the possible effects of montelukast against doxorubicin-induced nephrotoxicity in rabbits.
Material &Methods: This study was carried out on eighteen rabbits of both sex weighing between 1000-1500 gm, they were equally divided into three groups: control group: received (5ml) of isotonic saline i.p. at day3.Doxorubicin group: treated with single dose of doxorubicin (25 mg/kg i.p.)at day 3. Montelukast prophylaxis and treatment group: treated with montelukast (10mg/kg oral) for 3 days before and two days after a single injection of doxorubicin. All animals were sacrificed at day 5. Changes in serum urea, creatinine, total protein and albumin were evaluated .In addition, glutathione and malondialdehyde of kidney tissues were measured. Finally histopathology changes scores of kidney for all groups were examined.
Result: Doxorubicin administration resulted in a significant increment of serum urea and creatinine and kidney tissues malondialdehyde levels while significant reduction of serum levels of total protein and albumin and kidney tissues glutathione levels compared to that of control group. Histopathological changes scores showed a moderate score level compared to control group ($P \leq 0.05$). Montelukast prophylaxis and treatment group showed a significant elevation in serum urea and creatinine and kidney tissues malondialdehyde whereas a significant reduction in seum albumin and tissue glutathione in kidney tissue, at $P \leq 0.05$.
Conclusion: According to the results obtained from this study one can conclude the montelukast ability to potentiate doxorubicin nephrotoxicity.

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Introduction

The anthracycline antibiotics (ANT) are isolated from <u>*Streptomyces peucetius*</u> and widely used as cytotoxic anticancer drugs [1, 2]. The introduction of ANT to the chemotherapy of malignant neoplasms has been one of the major successes of cancer medicine. The anthracyclines [doxorubicin(DOX), daunorubicin, epirubicin and idarubicin] are one of the most clinically useful groups of anticancer chemotherapeutics. These drugs are routinely employed in combination regimes with other groups of drugs in which each drug generally exhibits a different mechanism of action to increase tumor cell kill and to minimize induced resistance to these drugs [3]. Molecular mechanisms of

DOX account for both its anti-cancer and its toxic effects (in the heart, brain, kidney, etc.) and it acts at two fundamental levels: altering DNA and producing free radicals[4].Intercalation into DNA [5]; Topoisomerase II Inhibition[20]**.** The addition of one electron to the quinone moiety of ring C of DOX as in figure (1- 3) results in the formation of a semiquinone form that quickly regenerates the quinone form, by reducing molecular oxygen to ROS such as hydrogen peroxide (H_2O_2) , superoxide anion ($O_2 \bullet^-$) and hydroxyl free radical ($OH^\bullet$) in the presence of nicotinamide adenine dinucleotide phosphate NAD(P)H oxido-reductases(cytochrome P450, mitochondrial NADH-dehydrogenase, xanthine dehydrogenase and endothelial nitric oxide synthase), which attack and oxidize DNA[6]. NAD(P)H oxidases activation may generate peroxynitrite free radical($ONOO^{\bullet-}$) through the reaction of mitochondrial $O_2 \bullet^-$ and with nitric oxide [7]. Iron can react with DOX and formation of DOX-iron complex which is highly toxic to membrane lipids, proteins and DNA [8, 9]**.**The renal toxicity of DOX may be due to alterations of the permeability of the glomerular capillary wall or to the consequence of oxidative stress such as oxidation and cross-linking of cellular thiols and membrane lipid peroxidation [10]. Indeed, DOX-induced nephropathy, the glomerular cells produce reactive oxygen species which cause glomerular injury. ROS may directly damage lipid membranes and they may also mediate the activation of genes for some proinflammatory cytokines (TNF-alpha, IL-1 and IL-6) through stimulation of transcription factor nuclear factor kappa B (NF-kB) [11] .

Montelukast (MK), the selective LTD4 receptor antagonist, is used mainly to reduce eosinophilic inflammation in asthmatic patients[12]. It is also effective in management of allergic rhinitis and chronic obstructive pulmonary disease [13]. The oral bioavailability of MK is 60–70%. It is over extensively bound to plasma proteins (99%) and its elimination half-life is 4–5 h. It's extensively metabolized to one major and several minor metabolites that are mainly excreted into bile [14, 15]. Montelukast was reported to have a protective effect in different models of renal injury in experimental animals. In a model of renal injury in rats, MK reversed ischemic/reperfusion-induced oxidant responses, improved microscopic damage and renal function by inhibiting neutrophil infiltration, balancing oxidant-antioxidant status and regulating the generation of inflammatory mediators[16].

The same protective effect of MK was observed in pyelonephritic rats in a model of *Escherichia coli*-induced oxidative injury and scarring in renal tissue suggesting a future role for $CysLT_1R$ antagonists in the treatment of pyelonephritis [17] . It was reported that MK ameliorated chronic kidney toxicity induced by cyclosporin [18].
MK may be a beneficial remedy for deleterious changes in kidney function parameters and oxidative stress markers induced by cisplatin treatment[19].

Kose et al. (2012) demonstrated the therapeutic effects of MK against amikacin-induced acute renal damage by reducing the oxidative damage and renal dysfunction [20]. MK was also able to prevent rhabdomyolysis-induced acute renal failure in rats [21].

Animals & Experimental

Eighteen domestic rabbits were randomly divided into three groups, each of six rabbits as follow: **Group1 (**Control group): rabbits were received of (5ml/kg i.p.) at day 3, then animals were sacrificed at day 5.**Group2 (**DOX group): rabbits were received a single dose of DOX (25mg/kg i.p.)[22, 23] at day 3, then animal were sacrificed at day 5.**Group3**(MK prophylaxis and treatment group): rabbits were treated with MK (10mg/kg/day orally)for three days prior and two days after single dose of DOX (25mg/kg i.p.) given at day 3, then animal were sacrificed at day 5.
The blood was aspirated from heart of rabbits after 48hr of DOX administration directly by intracardiac puncture and then centrifuged for 15-20 minutes at 3000(rpm)[24]. The supernatant was used for the estimation of serum urea, creatinine, total protein, and albumin. After the animals have been euthanize by anesthetic ether, kidneys were quickly excised, placed in chilled phosphate buffer solution (pH 7.4) at 4 ^{0}C, blotted with filter paper and weighed. One gram of organ was then taken to prepare 10% tissue homogenate using the same buffer solution utilizing tissue homogenizer[25] at set 3 for 1 minute at 4 ^{0}C. All preparations were freshly prepared and kept frozen (- 70 ^{0}C) unless worked immediately. Kidney tissues were prepared for histological examination according to the method of Junqueira et al. in 1995 [26]using paraffin sections technique.

Statistical Analysis

Statistical analysis was performed with the SPSS 20 statistical package for social sciences and Excel 2013. Descriptive statistics for the numerical data were formulated as mean and standard error mean (S.E.M.). Numerical data were analyzed using independent Student's t-test for comparison between two groups. Mann-Whitney U test for measuring of histopathological changes scores. The difference was considered significant when p value was $\leq$ 0.05 [27] .

Determination of Serum Urea

Serum urea levels were determined using urease-modified Barthelot reaction[28] by a ready-made kit for this purpose ,which can be measured spectrophotometrically at 580 nm. Levels of serum urea were expressed in mg/dl.

Determination of Serum Creatinine

Serum creatinine concentrations were determined according to Jaffe reaction using ready-made kit for this purpose [29] that can be measured at 500 nm. The red color intensity is directly proportional to creatinine concentration, which was expressed in mg/dl.

Determination of Serum Total Protein

Serum total protein was determined using Biuret colorimetric method[30].

Determination of Serum Albumin

Albumin concentration in the sample is proportional to the intensity of the color formed in the presence of bromcresol green [31].

Measurement of Lipid Peroxidation

Malondialdehyde (MDA), the end product of lipid peroxidation, was analyzed according to the method of Buege, and Aust [32] which is based on the reaction of MDA with thiobarbituric acid (TBA) to form MDA-TBA complex which can be quantitated spectrophotometrically.

Determination of Reduced Glutathione Level

Total thiol contents, which could be use as indicator for reduced glutathione (GSH), was determined according to the method of Elman's [33] that included dithio-nitro benzoic acid (DTNB) reagent [0.1mM DTNB in 0.1M phosphate buffer pH 8 (11.87gm di-sodium hydrogen phosphate, 9.073gm potassium dihydrogen phosphate in 1000ml of distilled water)]. The light absorbency of the solution at 412 nm was measured after 2 minutes.

Assessment of Histopathological Changes in Kidney Sections

The slides were coded and semi-quantitative analysis of the kidney sections was performed without knowledge of the treatment protocol [34, 35].

The changes seen were limited to the tubulointerstitial areas and graded as follows: 0 for (normal tissues) , 1 for (mild areas of lesion tubular epithelial cell swelling, vacuolar degeneration, necrosis, hyaline cast deposition and desquamation involving (25%) of cortical tubules), 2 for (moderate similar changes involving (25%) ,but less than (50%) of cortical tubules) , 3 for (high similar changes involving (50%), but less than (75%) of cortical tubules) and 4 for (very high similar changes involving (75%) of cortical tubules).

Results

Rabbits received a single dose of DOX (25 mg/kg i.p.) showed a significant elevation of mean serums urea and creatinine compared to the control group (p = 0.0001 and 0.001 respectively), [Table 1]. Whereas, serum levels of both total protein and albumin levels were significantly reduced as compared to the control group ($P \leq 0.05$), [Table 1]. Furthermore, animals treated with i.p. single dose of DOX (25 mg/kg) was revealing a significant elevation of the MDA in comparison to the MDA level of control group ($P \leq 0.05$). Also, there was a significant declined of GSH level when being compared to the GSH mean of control group ($P \leq 0.05$), [Table 1]. DOX group reveals a moderate tubular epithelial cells welling and vacuolation with glomerular congestion as shown in figure (2).

Effect of Montelukast Prophylaxis and Treatment on Doxorubicin Nephrotoxicity

MK prophylaxis and treatment group with once daily dose (10mg/kg) for three successive days before and two successive days after DOX administration caused a significant increment of urea level as compared to control group($P \leq 0.05$) whereas creatinine concentrations significantly raised in comparison with control and DOX groups ($P \leq 0.05$), [Table 1].

A significant reduction in serum total protein mean and albumin mean compared to control and DOX treated groups ($P \leq 0.05$), [Table 1]. The levels of MDA in MK prophylaxis and treatment group appear significantly raised level when compared to control and DOX groups ($P \leq 0.05$), [Table 1]. Whereas, the level of GSH revealed a significant reduction in comparison with control and DOX groups ($P \leq 0.05$), [Table 1].Marked glomerular capillary congestion with severtubularepithelialhydropicdegenerationwithvacuolation,tubularatrophy and tubular loss.

Table 1: Effects of montelukast on serums urea ,creatinine, total protein , albumin , tissue malondialdehyde and tissue glutathione against doxorubicin- induced nephrotoxicity.

Parameters	Control group	Doxorubicin group	Montelukast group
Serum Urea(mg/dl)	28.1 ± 1.9	71.8 ±3.5 [a]	121.5 ± 3.2 [a, b]
Serum Creatinine (mg/dl)	0.6 ±0.02	0.94 ±0.06 [a]	3.14 ±0.21 [a, b]

Serum Total Proteins (g/dl)	5.16 ± 0.31	4.38 ± 0.11 [a]	4.13 ± 0.21 [a, b]
Serum Albumin(g/dl)	2.26 ± 0.09	1.91 ± 0.10 [a]	1.56 ± 0.16 [a, b]
Tissue Malondialdehyde(μmol/g)	20.96 ± 1.7	56.29 ± 1.4 [a]	62.02 ± 1.2 [a,b]
Tissue Glutathione(μmol/g)	9.05 ± 0.4	2.7 ± 0.26 [a]	1.7 ± 0.2 [a, b]
Histopathological Changes Scores	0.0 ±0.0	2.33 ±.21[a]	3.50 ±0.22 [a, b]

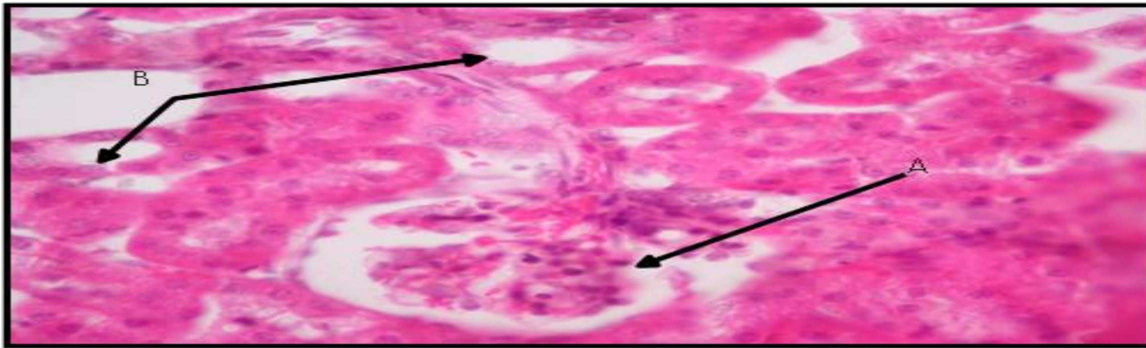

Figure1: Section of kidney of control group shows A) Single glomerular tuft, B) Proximal tubules appear with normal epithelial cells. H&E(40X).

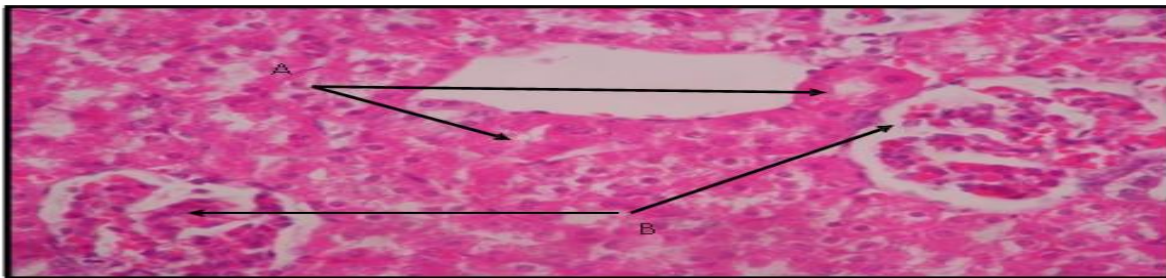

Figure (2): Section of kidney of (single dose 25mg/kg i.p.) DOX group reveals A) Moderate tubular epithelial cell swelling and vacuolation B) Glomerular congestion. H&E (40X).

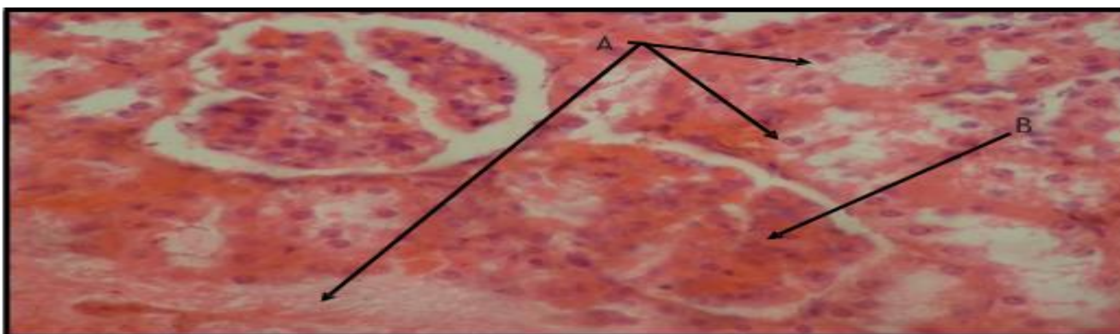

Figure3: Section of kidney of MK prophylaxis and treatment group (10mg/kg oral) for 5days with single dose of DOX(25mg/kg i.p.) shows A)Marked glomerular capillary congestion B)Severe tubularepithelialhydropicdegenerationwithvacuolation,tubularatrophy and tubular loss. H&E(40X).

Discussion:

This study was designed to explore the possible protective effects of each of MK on experimentally DOX-induced nephrotoxicity in rabbits. The nephrotoxic effect of DOX (25mg/kg i.p.) illustrated by elevation of serum urea and creatinine levels as compared to control group with significant reduction in both serum total protein and albumin which supported by histopathological changes in kidneys tissues including tubular epithelial cells welling, vacuolation and glomerular congestion . The elevation of serum urea and creatinine is observed after extensive renal damage and approximately half of the nephrons need to be damage[36]. The rate of rise of serum creatinine is dependent on many factors, including the new GFR rate of tubular secretion, rate of generation and volume of distribution[37, 38]. Once the initial free radicals increase after DOX administration, locally infiltrated neutrophils and activated glomerular mesengial cells continue free radical production [39, 40]. DOX induced inflammatory response of the tissue exhibited leukocytes accumulation in the renal tissue that led to production of hypochlorous acid which responsible for damaging and oxidizing proteins, amino acids, nucleic acids and lipids of kidney tissues[41]. DOX-induced glomerular injury or tubular injury and decreased reabsorption that demonstrated clearly by increment of urinary albumin and urine protein excretion and decrease in plasma total protein and albumin[42, 43]. The present study reveled histopathological features of DOX acute nephrotoxicity (tubular epithelial cells welling, vacuolation and glomerular congestion). In addition, enhanced lipid peroxidation is known to be one of the toxic manifestations of DOX administration and is measured in terms of MDA levels a lipid peroxidation marker with reduction of GSH level in tissues led to reduction in cellular defense compound against ROS. The results are consistent with previous reports that showed GSH concentration is decreased upon DOX–treatment [44-47].

When MK was administred before and after DOX showed a significant potentiation of nephrotoxicity by increment of lipid peroxidation end product (MDA) and depletion of GSH associated with deterioration of renal functions appeared on elevation of urea and creatinine levels with reduction in levels of serum total protein and albumin beside extensive and intensive histopathological changes scores. MK potentiation of toxicity may be attributed to induction of intrinsic apoptotic pathway [48]; transient vasoconstriction small arterioles [49] and may be due to lack of blocking the effect on LTB_4 could be important in interpretation of side effect probably associated inflammation[50] . The P-gp inhibitors effect of MK may increase intracellular accumulation of DOX which may enhance cytotoxic effects and/or systemic toxicity [51].

Conclusion

According to the results obtained from this study, one can conclude that Montelukast has the ability to potentiate DOX–induced nephrotoxicity at applied dose.

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