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Evaluation of the antioxidant protective effect of oxytocin and silymarin against gentamicin-induced nephrotoxicity in rat

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Gentamicin is an effective aminoglycoside antibiotic against severe infections. In spite of inducing nephrotoxicity and oxidative damage, gentamicin is used clinically due to its wide spectrum of activities against Gram negative bacterial infections. Its nephrotoxicity occurs by selective accumulation in renal proximal convoluting tubules. Its nephrotoxicity involves renal free radical generation and reduction in antioxidant defense mechanisms. A potential therapeutic approach to protect or reverse gentamicin-induced oxidative stress and nephrotoxicity would have more importance for clinical consequences. Therefore, the present study was designed to investigate the possible antioxidant protective effects of oxytocin and silymarin against gentamicin-induced renal damage in rats. A total of 40 adult male albino rats were divided into four groups. The first group is the control group that received normal saline (1ml/kg/i.p/day for 8 consecutive days), the second group was treated with gentamicin (80mg/kg/i.p/day for 8 days), the third group was treated with gentamicin (80mg/kg/i.p/day for 8 days) and oxytocin (5 I.U/kg/i.p/day for 8 days) and the fourth group was treated with gentamicin (80mg/kg/i.p/day for 8 days) and salymarin in a dose of (50 mg/kg orally/day for 8 days). Some biochemical and histopathological examinations of kidneys were performed after treatment for evaluation of the oxidative stress and renal nephrotoxicity. Gentamicin treatment significantly increased serum urea and creatinine levels and AST activities. Also gentamicin significantly decreased the total antioxidant capacity and catalase activity in renal tissues. Renal tissue malondialdehyde (MDA) has a non significant increase, while renal reduced glutathione (GSH) wasn't changed. Study of renal morphology showed degenerative changes in the form of cloudy swelling, hydropic degeneration and glomerular necrosis in gentamicin group. Administration of oxytocin and silymarin with gentamicin ameliorated to some degree the biochemical changes and oxidative stress parameters against gentamicin-induced nephrotoxicity. It was concluded that treatments with these antioxidants could have beneficial effects in treatment of gentamicin induced nephrotoxicity.

Gentamicin is an aminoglycoside antibiotic widely used in veterinary and human clinical practice for the treatment of Gram-negative bacterial infections. Treatment with gentamicin often associated with an induction of nephrotoxicity, which is seen in 10–20% of patients of acute renal failure (Ali, 1995). Despite the introduction of newer and less toxic antibiotics, gentamicin continues playing a useful role in the treatment of serious enterococcal, mycobacterial and Gram-negative infections, due to its effectiveness against resistant β-lactamic microorganisms, its low cost, and the low levels of resistance among members of Family Enterobacteriaceae (Edson and Terrell, 1999). Gentamicin accumulates in the renal cortex and induces renal morphological changes characterized by tubular necrosis, which is localized mainly in the proximal tubules and an overall syndrome very similar in humans and experimental animals. The effects of gentamicin on biological membranes appear to be important in its toxicity. Gentamicin undergoes partial re-absorption by proximal tubular cells by adsorptive endocytosis that results in the fusion of endocytic vacuoles with lysosomes where the drug accumulates. This accumulation induces the process of lysosomal phospholipidosis, resulting in tubular necrosis, which is a key

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pathological mechanism contributing to renal toxicity (Pitchai *et al*., 2010). The other important mechanism which involved in gentamicin nephrotoxicity is the generation of reactive oxygen species (ROS) (Kadkhodaee *et al*., 2005). Gentamicin directly increases the production of mitochondrial ROS from the respiratory chain (Morales *et al*., 2010). Many strategies have been reported to ameliorate gentamicin nephrotoxicity in experimental animals which focused on the use of various antioxidants (Ali, 2003).

Oxidative stress represents a major common pathway of cellular injury (Sohal, 2002).

Antioxidants in general show marked nephroprotective activites against gentamicin-induced nephrotoxicity. Therefore, many products reported to have antioxidant potentials possess nephro-protective potentials, these include for example Nigella sativa (Yaman and Balikci, 2010), grape seed extract (Safa *et al*., 2010), green tea extract (Sara *et al*.2009), vitamin E and N-acetyl cycteine (Patel *et al*., 2011) and sesame oil (Periasamy *et al*., 2010).

Silymarin, an antioxidant flavonoid complex isolated from the seed of Silybum marinum (milk thistle) possesses a powerful free radical scavenging properties (Kren and Walterova, 2005). In addition, silymarin regulates the intracellular contents of the reduced glutathione (GSH) (Borsari *et al*., 2001). Silymarin is used clinically to treat chronic inflammatory liver disease and hepatic cirrhosis. Recuperative effect of silymarin on the renal tissue damage may be related to an increase in the activity and recovery of gene expression of antioxidant enzymes which in addition to the glutathione system constitute some of the most important defense mechanisms against free radicals damage (Soto *et al*., 2010).

Oxytocin (OT) is a neurohypophysial nonapeptide synthesized in the paraventricular and supra optical nuclei of the hypothalamus (Olson *et al*., 1992). Its receptors are widely distributed in the central nervous system and have been identified in the kidney heart, thymus and pancreas (Gimple and Fahrenholz, 2001). Oxytocin has antioxidant properties and modulates the immune and anti-inflammatory response in wound healing and sepsis induced animal models after subcutaneous injection. (Işeri *et al*, 2005).

The present study examined the protective antioxidant effects of silymarin and oxytocin on gentamicin-induced nephrotoxicity. Some biochemical parameters for renal assessment and histopathological examination of kidney also performed. It is a new trial. There protective antioxidant properties were recorded previously against experimental gentamicin nephrotoxicity in dogs and cisplatin nephrotoxicity in rat respectively.

Material and methods

Drugs.

Gentamicin-sulphate (GARAMYCIN®) was obtained commercially as AN injectable solution produced by Schering-Plough (U.S.A).

Oxytocin (Syntocinon®) was obtained commercially as injectable solution produced by (Novartis Pharam).

Silymarin (Legalon®) a commercially product produced by MAdAUS GmbH. (Germany).

Experimental animals. Forty adult male albino rats weighed (170±30 g) were supplied by the Egyptian Organization for Biological Products and Vaccines. They had free access to water *Ad libitum* and a normal rat chow diet. The animals were housed 5 rats per cage.

Experimental design. One week after acclimatization, the rats were randomly divided into four experimental groups (10 rats in each); the first was considered as the (C) control group, they injected intraperitoneally (i.p) with 0.9% NaCl (1ml/kg/day/for 8 days). Whereas, the second one (gentamicin group, G) received gentamicin alone (80 mg/kg/i.p/day for 8 consecutive days), (Patel, *et al*., 2011). The third one (GO group) received the same previous dose of gentamicin in addition to oxytocin (5 I.U/kg/i.p for 8 consecutive days), (British pharmacopoeia, 1985). The fourth one (GS group) received the same previous dose of gentamicin in addition to silymarin orally using gavage (50 mg/kg/day for 8 consecutive days, (Gholamreza *et al*., 2005). Twenty four hours after the last doses of treatments, blood samples were collected via retro-orbital bleeding for serum separation and storage at -80 ˚C for further biochemical analysis. Rats were then sacrificed and kidneys were removed for histological and biochemical studies.

Renal tissue homogenate preparation. Animals were sacrificed and kidneys were immediately removed and washed using chilled saline solution (0.9%). One gram of kidney was, homogenized in 5 ml phosphate buffer saline (pH 7.4), and then centrifuged at 3000xg for 15 min at 4˚C. The supernatant was collected and stored at -80˚C for further analysis.

Biochemical parameters for renal function assessment. Serum urea level and serum creatinine level were determined according to Yong (2001) by using commercially available kits (Diamond, Cairo, Egypt). Activity of aspartate amino transferase (AST; EC 2.6.1.1) was determined according to Bergmeyer *et al*. (1977) using commercially available kits (BioSystems S.A, Barcelona, Spain).

Determination of some antioxidant parameters and lipid peroxidation in kidney tissue homogenate. Antioxidant parameters including total antioxidant capacity (TAC), reduced glutathione (GSH) and catalase activity were measured in kidney tissue homogenate using commercially available kits (Bio-diagnostic, Cairo, Egypt), according to Koracevic *et al*. (2001); Beutler, *et al*. (1963) and Aebi (1984) respectively. Also lipid peroxidation (malondialdehyde (MDA) was measured according to Ohkawa *et al*. (1979) by using of the commercially available kits (Bio-diagnostic, Cairo, Egypt).

Histopathological exanimation. Kidneys were sectioned and fixed in 10% formalin and then embedded in paraffin. Sections were cut at 7 µ and stained with haematoxylin and eosin and then examined using light microscope, according to Bancroft and Steven (1983).

Statistical analysis. Statistical analysis was carried out using GraphPad Instat software (version 3., ISS-Rome, Italy). Unless differently specified, groups of data were compared with un-paired t-test and one-way analysis of variance (ANOVA) followed by Tukey-kramer (TK) multiple comparisons post-test. Values of $P<0.05$ were regarded as significant. The data, as clearly indicated are reported in tables as mean ± standard error (S.E).

Results

Protective effect of oxytocin and silymarin on getamicin induced nephrotoxicity.

Gentamicin administration to rats resulted in significant increase in serum urea, creatinine levels and AST activity in all groups of rat in comparison to control. Administration of oxytocin and silymarin significantly reduced these elevations to a certain degree in comparison to gentamicin alone. It was obvious in GO group. The result was presented in table (1).

Table (1): Effect of gentamicin, oxytocin and salymarin on serum parameters of kidney function in control and experimental groups of rats.

Group	Control	Gentamicin (G)	Gentamicin+ Oxytocin (GO)	Gentamicin+ Silymarin (GS)
Urea (mg/dl)	37.7± 2.59	77.8 ± 6.6***	51.46± 1.89* [a]	63.19 ± 4.44** [b]
Creatinine (mg/dl)	0.49 ± 0.14	1.24 ± 0.13*	0.99 ± 0.19*	1.2 ± 0.17*
Serum AST (U/L)	32.53 ± 2.87	45.16 ± 5.3*	25.14 ± 1.58 [b]	20.78 ± 3.12 [a]

*** significantly different at $p<0.001$ from control, ** significantly different at $p<0.01$ from control
* significantly different at $p<0.05$ from control. [a] significantly different at $p<0.01$ from gentamicin group and [b] significantly different at $p<0.05$ from gentamicin group.

Effect of oxytocin and silymarin in combination with gentamicin on some antioxidant parameters and lipid peroxidation in renal tissue.

Gentamicin administration resulted in a significant decrease in TAC and catalase enzyme in renal tissue homogenate of all groups of rat in comparison to control. Reduced glutathione not changed; while MDA was increased none significantly in the G and GO groups respectively.

Histopathological examination of renal tissue.

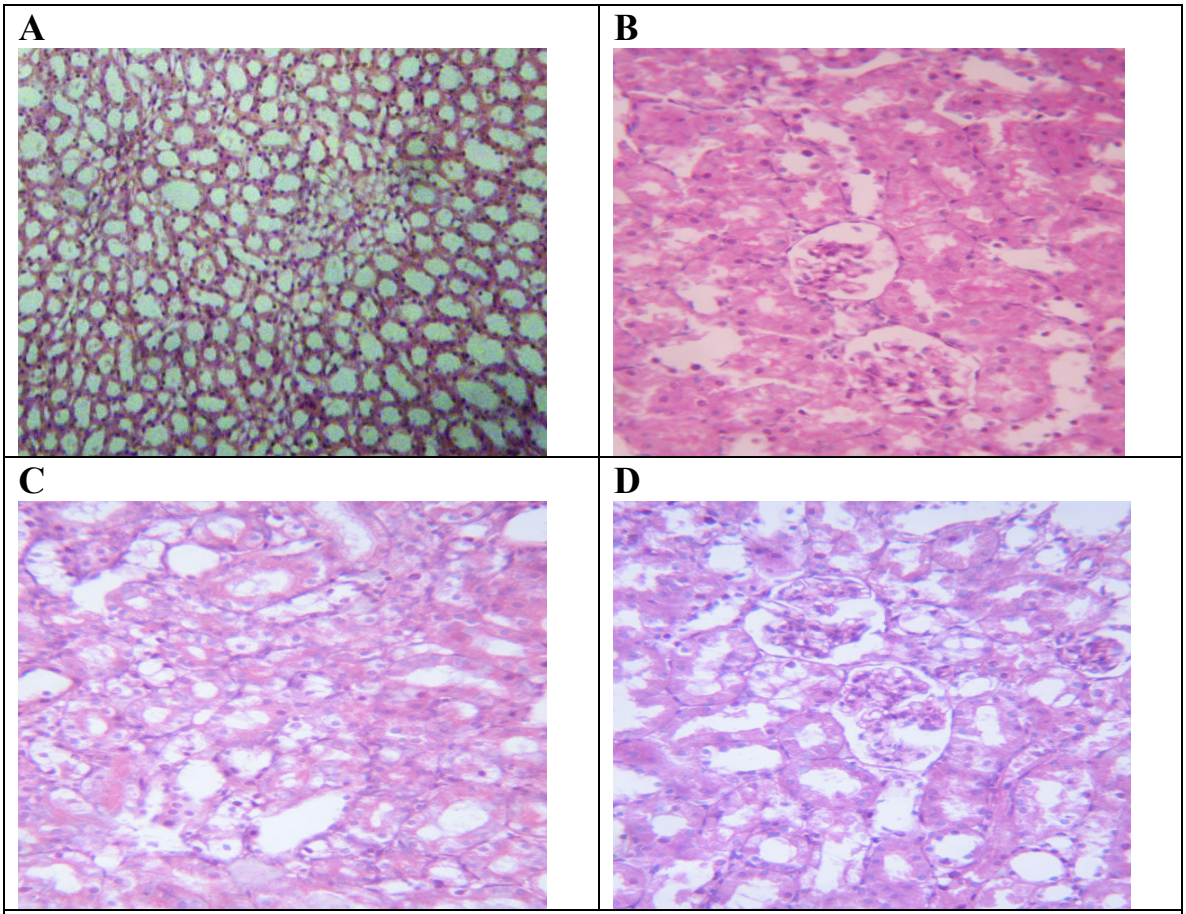
Light microscopic examination of renal cortex of control rats showed numerous renal corpuscles and tubules. Each renal corpuscle was formed of a tuft of glomerular capillaries surrounded by Bowman's capsule with outer parietal layer of simple squamous epithelium and inner visceral layer surrounding the glomerulus. The two layers were separated by narrow urinary space (Photo A). Light microscopic examination of the renal cortex of (G group) revealed degenerative changes in the form of cloudy swelling and hydrophobic degeneration. Glomerular necrosis was clear. Hyaline castes were present in the tubular lumen (Photo B). Light microscopic examination of the renal cortex of (GO group), Photo (C) showed the same histopathological picture as the (G group) but with less extensive degree. Renal

cortex of (GS group) showed degenerative changes but with less necrotic changes in comparison to (G and GO groups) as showed in (Photo D).

Table (2): Effect of gentamicin, oxytocin and silymarin on some antioxidant parameters and lipidperoxidation in control and experimental groups of rats.

Group	Control	Gentamicin (G)	Gentamicin+ Oxytocin (GO)	Gentamicin+ Silymarin (GS)
TAC (nM/g tissue)	2 ± 0.08	1.65 ± 0.11*	1.49 ± 0.07**	1.69 ± 0.04*
GSH (mg/g tissue)	14.16 ± 1.72	14.09 ± 0.79	15.27 ± 1.93	14.58 ± 1.18
Catalase (U/g tissue)	0.69 ± 0.1	0.28 ± 0.06**	0.25 ±0.03***	0.37± 0.04*
MDA (nmol/g tissue)	22.92 ± 1.59	26.42 ± 2.71	24 ± 1.3	18.1± 0.83

***significantly different at p<0.001 from control, ** significantly different at p<0.01 from control and * significantly different at p<0.05 from control



(Photo A) Light microscopic examination of the renal cortex of Control group. (Photo B) showed the light microscopic examination of the renal cortex of (G group). (Photo C) and (Photo D) showed the light microscopic examination of the renal cortex of (GO &GS groups) respectively.

Discussion

It is known that aminoglycosides (especially GM) can cause nephrotoxicity. It has been estimated that up to 30% of the patients treated with aminoglcosides for more than 7 days showed some signs of nephrotoxicity. Many antibacterial drugs with equal and sometimes better sensitivity and safety profiles than aminoglycosides are available, but the latter drugs still remain a clinically important group

of antibiotics as they have an excellent antibacterial profile against Gram-negative life-threatening infections, and there is more experience with these than with the other newer antibacterial drugs.

In experimental animals, several strategies to ameliorate the toxicity have been attempted. These include controlling the time of administration of the antibiotics and co administering agents to mitigate the renal toxicity. In view of their excellent safety and efficacy profiles, antioxidant drugs were found to produce the best nephroprotection as reviewed by (Koyner *et al*., 2008). In this study we used two types of antioxidant drugs. One is hormonal (oxytocin) and the other is a medicinal plant (silymarin) as a new trial to mitigate gentamicin nephrotoxicity.

The present study indicated that marked significant elevations of serum urea, creatinine concentrations and also AST activity were evident suggesting a significant functional impairment of kidney in gentamicin-induced group. Similar pattern of changes were also observed by (Lafayette *et al*., 2001; Othman *et al*., 2010; Yaman and Balikci 2010). Administration of oxytocin or silymarin with gentamicin significantly decreased the elevation of serum urea, creatinine concentrations and also AST activity in comparison with gentamicin alone. This was obvious in the GO group indicating somewhat protection against gentamicin nephrotoxicity, these findings similar to results obtained by (Laila *et al*., 2011).

Similar results suggested that silymarin protected against cisplatin-induced renal toxicity (Karimi *et al*. 2005) and against adriamycin induced cardiotoxicity and nephrotoxicity in rats (Nagla *et al*., 2008).

Several mechanisms are involved in gentamicin-nephrotoxicity. One of these mechanisms is the increase of reactive oxygen species (ROS) generation. These radials include hydroxyl radicals and hydrogen peroxides in the renal cortex that eventually change antioxidant levels within the renal tissue and lead to structural and functional deterioration (Pedraza-Chaveri, 2000; Maldonado *et al*., 2003). In our study this indicated by significant decrease of total antioxidant capacity and catalase enzyme of renal tissue homogenate in the all groups which administrated by gentamicin specially the GO group. This indicated oxidative stress due to consumption of TAC and catalase enzyme in converting the toxic radicals to non-toxic end products (Shimeda *et al*., 2005).

Reduced glutathione serves as a scavenger of different free radicals and is one of the major defenses against oxidative stress (Rao and Shaha, 2001), any factor that leads to oxidative stress may result in GSH depletion due to consumption of the latter in counteracting free radicals and reactive oxidant intermediates (Ursini and Bindoli 1987).

In our study there was no significant variation of the renal homogenate level of reduced glutathione between all groups of rats. Our results agreed with Chao-Hen and Jerry (1982), Soejima *et al*. (1998) and Karahan *et al*. (2005), but another studies stated that gentamicin caused a decrease in renal glutathione levels in rats (Enver, 2003). These differences may be due to the doses of gentamicin used and period of administration.

The increases in the levels of lipid peroxidation products such as MDA are indices of membrane lipid damage (Kalpana *et al*., 2009).

Most of previous studies reported that gentamicin caused increases in renal MDA levels as an index of lipid peroxidation. In our study administration of gentamicin alone or with oxytocin increase the level of renal MDA but this was not significant in comparison with control group (Enver *et al*., 2003). Some scientific papers reported that in tissue neither MDA determination nor TBA-test response can generally be regarded as a diagnostic index of the occurrence extent of lipid peroxidation, fatty hydroperoxide formation, or oxidative injury to tissue (Janero, 1990; Ayşen *et al*., 2000). Another study reported that oxytocin prevented both lipid peroxidation and GSH depletion in the renal tissue invaded by bacteria, (Nes *et al*. 2006). Results in Table (2) showed that administration of silymarin protected to some degree the gentamicin depletion of antioxidant, this is similar to result detected by (Varzi *et al*., 2007) who found that Silymarin and vitamin E decreased gentamicin-induced nephrotoxicity in dogs.

In the present work the histological examination of the renal cortex revealed degenerative changes in the form of cloudy swelling, hydropic degeneration, glomerular necrosis and hyaline casts in the tubular lumen in gentamicin treated group. These changes appear to be less severe in the oxytocin and silymarin treated groups. This result was agreed

with result revealed by (Srinivasan *et al*. 2009) who find that gentamicin caused sever tubular necrosis, glomerular atrophy and severe extensive damage in kidney. Also the result was agreed with the result obtained by (Pitchai *et al*., 2010; Laila *et al.*, 2011) who found that oxytocin decrease the degenerative changes occurred by cisplatin-induced nephrotoxicity. Also treatment with oxytocin resulted with the reduction of glomerular atrophy and inflammation, which was limited to local sites (Nes *et al*., 2006).

Conclusion

Our study showed that oxytocin administration with gentamicin mitigated to some degree the nehphrotoxic effect of gentamicin on serum renal function parameters represented by urea, creatinine and AST. While silymarin administration with gentamicin minimize to some degree the depleting effect of gentamicin on total antioxidant capacity and the catalase levels of renal tissue. We suggest that these antioxidants should be administrated enough time before the beginning of gentamicin treatment and then continued with it in an attempt to induce significant effects.

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تقييم التأثيرالتأكسدى الوقائى لكل من الأوكسيتوسن والسليمارين ضد التسمم الكلوى بالجنتاميسين فى الجرذان

استهدفت هذه الدراسة معرفة التاثير التأكسدى الوقائى المحتمل الاوكسيتوسن و السليمارين ضد سمية الكلية المحدثة باستخدام عقارالجنتاميسين. تمت الدراسة على عدد٤٠ جرز تم تقسيمهم إلى أربعة مجاميع كل مجموعة مكونة من ١٠ جرذان المجموعة الاولى كانت مجموعة ضابطة تم حقنها بمحلول ملح فسيولوجي ٩, ٠% فى الغشاء البروتونى يوميا لمدة ٨ أيام والمجموعة الثانية تم حقنها بالجنتاميسين بجرعة ٨٠ مجم/ كجم /يوميا/ فى الغشاء البروتونى / لمدة ٨ ايام ، أما المجموعة الثالثة تم حقنها بالجنتاميسين بنفس الجرعة بالاضافة الى الاوكسيتوسن بجرعة ٥ وحدات دولية / كجم / اليوم / لمدة ٨ ايام ؛ والمجموعة الرابعة تم حقنها بالجنتاميسين بنفس الجرعة بالإضافة الى السليمارين بجرعة (٥٠ مجم / كجم / عن طريق الفم / يوميا ولمدة ٨ايام). وقد تم تقيم الضرر الكلوى المحدث بالجنتاميسين و أيضا تقيم التأثير الوقائى للعقاقير المختبرة بقياس تأثير كلا منهم على الوظائف الحيوية للكلى وذلك من خلال قياس معدل نشاط إنزيمات النقل الامينى AST وقياس مستوى اليوريا والكرياتينين فى الدم وكذلك قياس المؤشرات الحيوية للاجهاد التاكسيدى وقد تم دراسة التغيرات التشريحية المرضية فى أنسجة الكلى. أوضحت النتائج أن الجنتاميسين سبب ضررا بالغا فى الكلى والذى تبين من ارتفاع دلالات وظائف الكلى و الدلالات الحيوية للاجهاد التأكسدى مما أدى إلى تدمير النسق الطبيعى للكلى. كما قدم كل من الأوكسيتوسن والسليمارين كفاءة فى الوقاية من الأذى المحدث بواسطة الجنتاميسين و ذلك من خلال قدرتهم المضادة للأكسدة ومن خلال تقليل التغيرات االتشريحية المرضية فى أنسجة الكلى.