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ASSESSMENT THE EFFECT OF CAPTOPRIL, NIFEDIPINE AND THEIR COMBINATION ON GENTAMICIN INDUCED NEPHROTOXICITY IN RATS.

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ABSTRACT

This study is aimed to evaluate the effect of captopril (an ACE inhibitor), nifedipine (calcium channel blocker) and their combination on gentamicin induced nephrotoxicity. Captopril in a dose of 25mg/kg, nifedipine(20mg/kg) and their combination were orally administered to male albino rats for 6 days before and for 7 days along with gentamicin injection (80mg/kg, IP). At the end of the study, body and kidney weights were recorded. Serum creatinine, blood nitrogen urea, albumin, lactate dehydrogenase (LDH) sodium and calcium levels were measured. In addition renal lipid peroxidation represented by malondialdehyde (MDA) and renal reduced glutathione (GSH)were also estimated. Histopathological examination of the kidney was also performed. Results of the present study showed that gentamicin induced significant increase in kidney weight, serum creatinine, blood nitrogen urea, and LDH levels. On the other hand serum sodium levels were reduced. Renal MDA was elevated and reduced GSH was significantly decreased in kidney tissues. Histopathological examination showed renal damage indicated by severe hydropic degeneration or focal necrosis and mild interstitial lymphocytic aggregations. Captopril reduced serum creatinine and increased kidney GSH content. It also reduced histopathological changes. Nifedipine decreased serum creatinine, urea and renal MDA levels. It increased serum sodium and calcium levels and renal GSH content. Histopathological examination showed that nifedipine modulated renal damage induced by gentamicin. However, captopril and nifedipine combination increased serum urea, creatinine and calcium levels and renal MDA levels. It reduced serum sodium levels. Histopathpathological examination demonstrated severe damage manifested by diffuse coagulative necrosis in all segments of the nephron in both cortex and medulla. In conclusion both captopril and nifedipine when used alone exerted a protective effect against gentamicin–induced nephrotoxicity .Nifedipine was better than captopril in this regard. However, their combination has a deleterious effect and exacerbated gentamicin–induced nephrotoxicity. The underlying mechanism(s) of this negative interaction needs further investigation.

INTRODUCTION

Nowadays, drug induced kidney disorders have become a frequent health problem. Iatrogenic nephropathies including acute renal failure (ARF) (20%) are one of the major negative prognostic factors in the internal disorders [1].

Gentamicin and other aminoglycosides which are useful in the management of Gram negative bacterial infections belong to those types of drugs. Their nephrotoxic effect may limit prolonged administration. They represent a major cause of ARF in hospitalized patients occurring in 10-20% of them [2].

Treatment of rats with gentamicin resulted in renal damage evidenced by proteinuria, polyuria and decreased creatinine clearance. Gentamicin also increased kidney angiotensin converting enzyme (ACE) levels [3].

Activation of the rennin angiotensin system (RAS) and the ensuing local vasoconstriction appear to be primarily responsible for the decrease in glomerular filtration [4].

It was observed that in patients with essential hypertension an unfavorable pattern of RAS may contribute to an increased risk of the development of renal failure [5].

However, ACE inhibitors like captopril were found to reduce blood pressure and provide end organ protection but may induce renal function deterioration. In these cases it was found that serum creatinine can be normalized by ACE inhibitors withdrawal [6].

On the other hand Pisoni et al., [7] reported that ACE inhibitors that are of proven benefit in the treatment of hypertension, congestive heart failure or acute myocardial infarction also offer significant renoprotection in both diabetic and nondiabetic individuals. Others showed similar observations [8].

In addition, calcium channel blockers have demonstrated a clear beneficial effect on renal vasoconstriction induced by cyclosporine therapy in renal transplantation patients and in prevention of ARF secondary to administration of radio contrast agents, amphotericin B, cisplatin and aminoglycosides [9].

Some experimental studies have shown that calcium channel blockers could prevent ischemic or toxic acute renal failure [10-13]. But others showed that they have no use [14-16] or exhibit a deleterious effect on renal failure[17].

Due to this controversy, this study was designed to investigate the effect of captopril as an example for ACE inhibitors, nifedipine as an example for calcium channel blockers and their combination on gentamicin induced acute renal failure. Our study also aimed to shed the light on the underlying mechanism of the protective effect if any exist.

Experimental :

Animals and Experimental design:

Thirty adult male albino rats (obtained from the National Research Centre, Cairo, Egypt.)weighing 180-200gm was used in the present study. They were housed 6 rats/cage with wood shave bedding and kept under constant environmental conditions throughout the experiment with free access to food and water ad libitum.After one week of accommodation period, they were randomly divided into 5 groups (6 rats/group) as following:

Group 1 (normal control): were given solvent only throughout the experiment.

Group 2 (gentamicin control): were given solvent orally for 6 days then injected

intraperitonealy with gentamicin in a dose of 80mg/kg for 7 days [18]

Group 3: were given captopril (25mg/kg) [19].

Group 4: were given nifedipine (20mg/kg) [20].

Group 5: were given captopril (25mg/kg) and nifedipine (20mg/kg)

Group 3,4 and 5 were given drugs once daily by oral route for 6 days before and 7 days along with gentamicin in the same previously mentioned dose.

Material:

Nifedipine was obtained from EIPICO Company (10th of Ramadan city, Egypt). Gentamicin was obtained from Memphis Company, Cairo, Egypt. Captopril was obtained from Bristol-Myers Squibb Egypt.

Sample collection:

Animals were fasted for 12 hours before sampling. Animals weight was recorded. Blood samples were obtained from the orbital sinus 24 hr after the last injection. Then animals were sacrificed by cervical dislocation. Serum was separated by centrifugation at 4000 rpm for 15 minutes. Part of serum was kept at -20C° for the assay of urea, creatinine, albumin, sodium and calcium levels. Another part of serum was used for determination of lactate dehydrogenase (LDH) at the same day. Both kidneys were rapidly isolated and weighed. One of them was chilled in liquid nitrogen thereafter it was homogenized in ice-cold saline to yield tissue homogenate. Reduced glutathione and MDA were determined in this homogenate. The other kidney was kept in 10 % formalin and processed for histopathological examination.

Methods:

Serum creatinine was determined by colorimetric method described by Henry et al., [21]. Blood urea was measured by enzymatic colorimetric method described by Patton and Crouch [22] using diagnostic kit supplied by Diamond Egypt. Serum albumin was measured according to the method of Doumas et al., [23] using Spectrum Diagnostic kit Cairo Egypt .Serum sodium and calcium was measured according to the method of Sarker and Chauhan [24] using Stanbio (USA) commercial kit. Reduced glutathione (GSH) was measured in 10% tissue homogenate according to the colorimetric method of Beutler et al., [25]. Malondialdehyde (MDA), as indicator of lipid peroxidation was measured in 10% tissue homogenate as described by Yoshioka et al., [26]. Serum LDH was determined in fresh serum using commercial kits (Elitech diagnostic, France) [27].

Statistical analysis:

It was performed using SPSS PC version 10 programs and graph pad program. Data are expressed as mean ± standard error of means (S.E.M.). Difference among groups was analyzed for statistical significance by one-way analysis of variance (ANOVA) .To show the difference among the groups; Turkey's post *hoc test* was used. Difference was regarded significant at probability level $P < 0.05$.

RESULTS

1-Effect of captopril, nifedipine and their combination on body and kidney weights in gentamicin treated rats:

Table 1 showed that there was a significant decrease in body weight in the combination group (168 ± 1.54 Vs 204 ± 2.16) when compared with normal control.Gentamicin induced a significant increase in kidney weight recording (0.596 ± 0.023 Vs 0.483 ± 0.021) when compared with normal control.

Table (1): Effect of captopril,nifedipine and their combination on body weight and kidney weight in gentamicin treated rats .

Groups	Body weight(gm)	Kidney weight(gm)
Normal control	204±2.16	0.483±0 021
Gentamicin(G)	184±6.37	0.596*±0.023
Captopril+G	200±6.64	0.610**±0 028
Nifedipine+G	190±9.6	0.532±0.027
Captopril+Nifedipine+G	168**±1.54	0.603**±0.01

Values are expressed as mean ± SEM .,(n=6animals).
* significantly different from normal control at p<0.05
** significantly different from normal control at p<0.01.

2-Effect of captopril, nifedipine and their combination on kidney function in gentamicin treated rats:

As shown in table 2, gentamicin caused a significant increase in both serum urea and creatinine recording (65±1.13 Vs 26.17±1.4 and 1.53±0.08 Vs 0.38±0.027) respectively when compared with normal control.

Nifedipine treatment significantly reduced both serum urea and creatinine levels in gentamicin treated rats recording (37±2.248 Vs 65±1.13 for urea and 0.76±0.058 Vs 1.53±0.085 for creatinine) when compared with gentamicin control.

Captopril did not significantly change serum urea levels but reduced serum creatinine levels significantly (0.8±0.17 Vs 1.53±0.085) when compared with gentamicin control.Captopril and nifedipine induced a significant increase in serum urea and creatinine (280.83±5.35 Vs 65±1.13 and 5.7±0.17 Vs 1.53 ± 0.085) respectively when compared with gentamicin control.

Table (2): Effect of captopril,nifedipine and their combination on serum urea and creatinine levels in gentamicin treated rats .

Groups	Urea (mg/dl)	Creatinine (mg/dl)
Normal control	26.17±1.4	0.38±0.027
Gentamicin(G)	65*±1.13	1.53*±0.085
Captopril+G	55±2.2	0.8@±0.17
Nifedipine+G	37©±2.248	0.76@±0.058
Captopril+Nifedipine+G	280.83©±5.35	5.7©±0.17

Values are expressed as mean ± SEM .,(n=6 animals).
* significantly different from normal control at p<0.001
@ significantly different from gentamicin at p<0.01.
© significantly different from gentamicin at p<0.001.

3- Effect of captopril , nifedipine and their combination on kidney MDA and reduced GSH in gentamicin treated rats:

Malondialdehyde (Table3) was significantly elevated in renal tissue in gentamicin treated rats (209.19±11.71 Vs 8.076±0.35) when compared with normal control. Nifedipine significantly reduced kidney MDA levels while nifedipine and captopril combination induced significant increase in kidney MDA levels (266.3±7.46 Vs 209.19±11.71) when compared with gentamicin control.

Table3 also demonstrated that gentamicin significantly reduced kidney GSH levels (21.4±0.9 Vs 46.9 ±1.24) when compared with normal control. Both captopril and nifedipine each alone increased kidney GSH levels (35.1±0.95 and 68.82±3.8 Vs 21.4±0.9) respectively when compared with gentamicin control. However, their combination had no significant effect on kidney GSH levels.

Table (3): Effect of captopril,nifedipine and their combination on kidney MDA and reduced glutathione(GSH) levels in gentamicin treated rats.

Groups	Kidney MDA(nmol/gm)	Kidney GSH(nmol/gm)
Normal control	8.076±0.35	46.9±1.24
Gentamicin(G)	209.19*±11.71	21.4*±0.9
Captopril+G	191.48±14.69	35.1@±0.95
Nifedipine+G	152.98@±8.58	68.82©±3.8
Captopril+Nifedipine+G	266.3@±7.46	27.59±2.12

Values are expressed as mean ± SEM .,(n=6 animals).
* significantly different from normal control at p<0.001
@ significantly different from gentamicin at p<0.01.
© significantly different from gentamicin at p<0.001.

3- Effect of captopril, nifedipine and their combination on serum albumin levels in gentamicin treated rats: Neither gentamicin nor other treatments had any significant effect on serum albumin levels as illustrated in Fig.1.

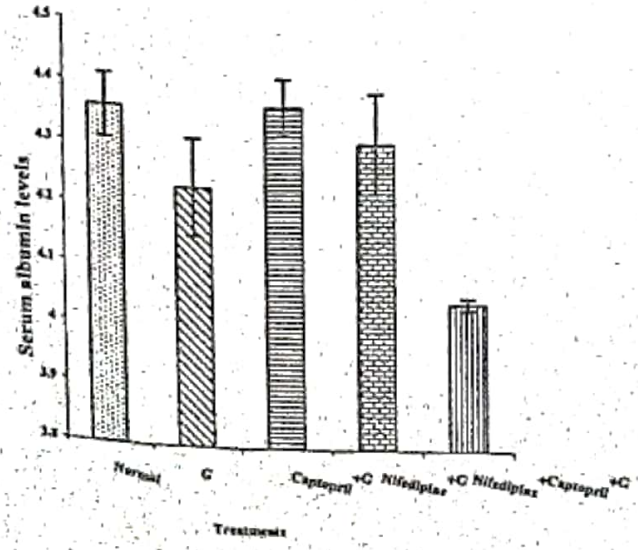

Fig.1 Effect of captopril, nifedipine and their combination on serum albumin levels of gentamicin treated rats. Values are mean±S.EM.,n=6.

4-Effect of captopril , nifedipine and their combination on serum LDH levels in gentamicin treated rats:

Gentamicin induced a significant elevation in serum LDH levels which was not affected by other treatments recording (1370.1±47.64 Vs1124.4±26.7) compared with normal control (Fig.2).

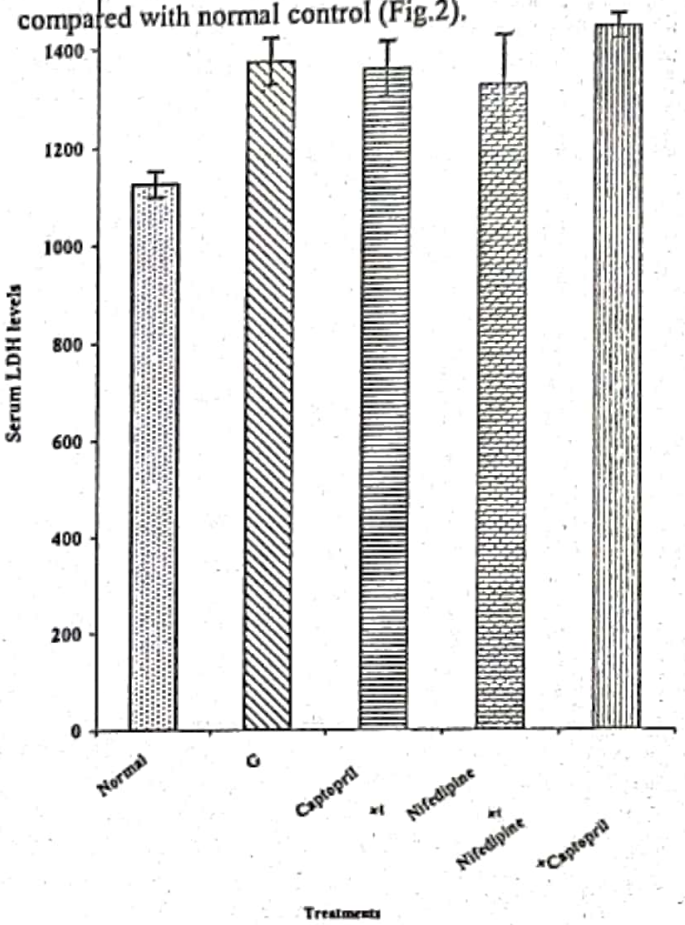

Fig. 2: Effect of captopril,nifedipine and their combination on serum LDH levels in gentamicin treated rats. Values are mean±S.EM., n=6. * significantly different from normal control at P<0.0

5- Effect of captopril , nifedipine and their combination on serum calcium and sodium levels in gentamicin treated rats:

As presented in Fig.3, gentamicin had no significant effect on serum calcium levels. Both nifedipine alone and in combination with captopril caused a significant increase in serum calcium levels recording (11.85±0.078 and 13.8± o.6 Vs 10.33± 0.046) when compared with gentamicin control.Fig.4 showed that gentamicin induced a significant decrease in serum sodium (147.02±0.4 Vs 151.1±0.33) compared with normal control.

Nifedipine induced a significant increase in serum sodium levels (150.3±0.62 Vs 147.02±0.4) when compared with gentamicin control. However, nifedipine combination with captopril caused a significant reduction in serum sodium levels

(135.45±0.45 Vs 147.02 ±0.4) when compared with gentamicin control.

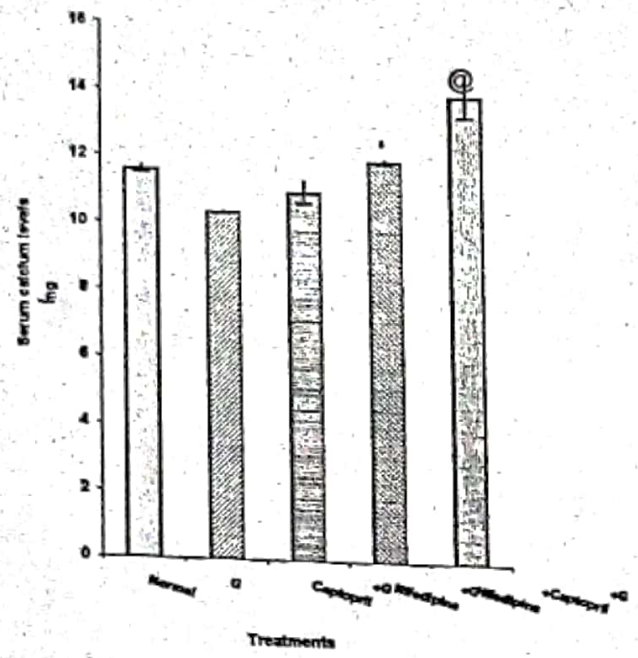

Fig.3 Effect of captopril, nifedipine and their combination on serum calcium levels in gentamicin treated rats. Values are mean ± S.EM.,n=6.
*significantly different from gentamicin at p<0.05.
@ significantly different from gentamicin at p<0.001.

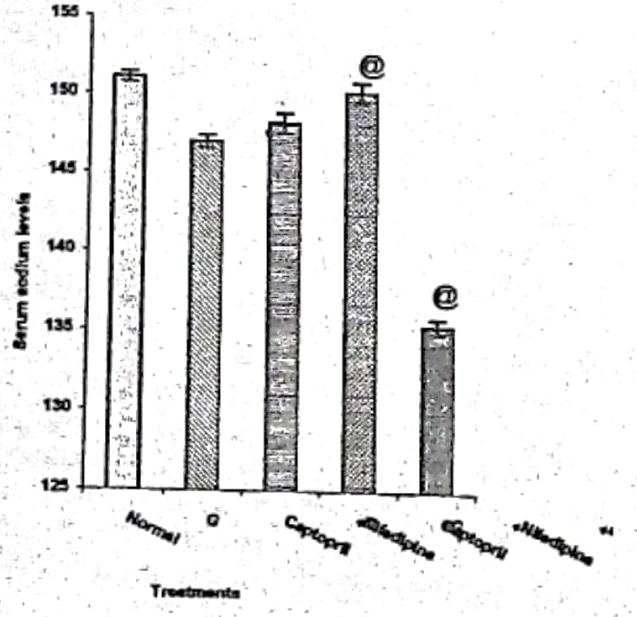

Fig.4:Effect of captopril,nifedipine and their combination on serum sodium levels in gentamicin treated rats . Values are mean±S.EM.,n=6.
*significantly different from normal at p<0.001.
@ significantly different from gentamicin at p<0.001.

6-Histopathological examination:

Examination of kidneys of normal rats showed that all segments of nephron and interstium in both renal cortex and medulla appeared normal (Fig.5). Gentamicin caused subcapsular nephrosis varied from severe hydropic degeneration to local coagulative necrosis with mild interstitial lymphocytic aggregations in renal cortex. Focal replacement of renal parenchyma with leukocytic aggregations mainly lymphocytes and histocytes were seen (Fig.6). Captopril treated group had necrotic changes in some renal tubules characterized by maintaince of architecture with cytoplasmic and nuclear changes and sometimes replaced by fibrous tissue (Fig.7).Other tubular epithelium suffered from degenerative changes. The kidneys of nifedipine treated rats suffered from degeneration of renal tubular epithelium with extravasted erythrocytes (Fig.8) A few glomeruli revealed hypercellularity with mild interstitial round aggregations. Edema and leukocytes were seen in renal medulla beside degenerative changes in some collecting tubules. Fig.9 showed that kidneys of rats treated with captopril/nifedipine combination had diffuse coagulative necrosis in all segments of nephron in both cortex and medulla with the presence of multiple large hyaline casts inside the Lumina were common.

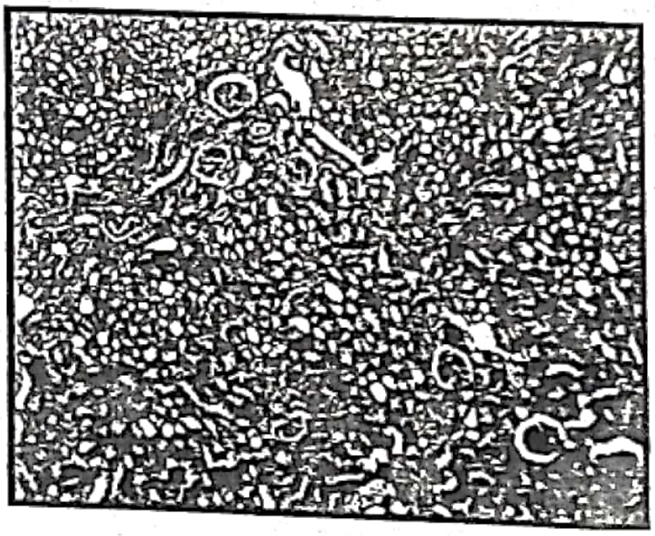

Fig.5 A photomicrograph of normal rat kidney showing normal nephron segments (H&E x1200).

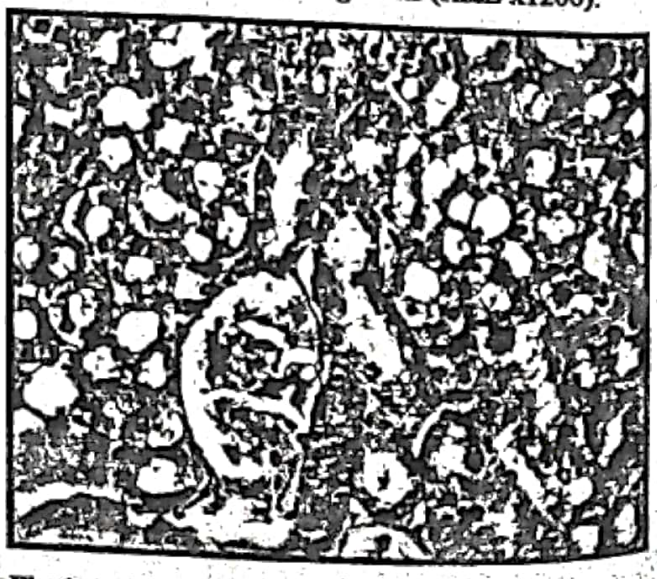

Fig.6 A photomicrograph of gentamicin treated rat kidney showing severe hydropic degeneration or focal

necrosis and interstitial lymphocytic aggregations (H&E x1200).

Fig.7 A photomicrograph of captopril treated rat kidney showing necrotic changes in some renal tubules and mild fibroblastic proliferation (H&Ex1200)

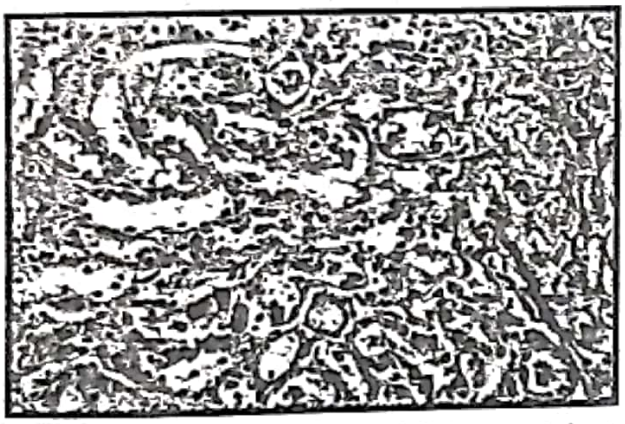

Fig. 8 A photomicrograph of nifedipine treated rat kidney showing degenerated tubular epithelium with extravasted erythrocytes. (H&Ex1200).

Fig.9 A photomicrograph of captopril/ nifedipine treated rat kidney showing diffuse coagulative necrosis with multiple hyaline casts in both cortex and medulla (H&E x1200).

DISCUSSION

Gentamicin induced nephrotoxicity limited its use. Results of the present study showed that gentamicin injection in a dose of 80mg/kg for 7 days induced both functional and structural damage of kidney. This is evidenced by the increase of urea, creatinine and kidney weight. In addition, gentamicin caused a significant decrease in serum sodium and kidney glutathione content .Gentamicin treatment induced a significant increase in lipid peroxidation as indicated by elevation of kidney MDAcontent.These functional impairment was associated with structural damage manifested by focal necrosis and lymphocytic infiltration.

These findings are supported by many previous studies [18, 28 29]. However Erdem et al., [30] who had different experimental design showed that gentamicin induced weight loss which is not shown in our study.The increase in kidney weight observed in our study is confirmed by the report of Lortholary et al., [13] who observed that aminoglycosides induced glomerular hypertrophy.

The mechanism underlying gentamicin nephrotoxicity is that gen. binds to the brush border membranes of renal tubules in its cationic form [31] by attaching to the acidic phospholipids then transferred to transmembrane megalin [32] Then it become internalized in endosomes then transferred to lysosomes where it binds to acidic phospholipids [33] causing lipid bilayers aggregations and phospholipase inhibition [34].Gentamicin also inhibits Na-K ATPase and increased natriuresis which is responsible for the reduction in sodium levels. Generation of free radicals and ACE activation also takes place.

The current study demonstrated that captopril an ACE inhibitor improved gentamicin induced nephrotoxicity as indicated by the decrease in serum creatinine and the increase in kidney GSH content and reduction of structural changes. However, this improvement is limited and not associated by complete recovery .These results disagree with the previous results of Macias-Nunez et al [6] who found that ACE inhibitors may induce deterioration of renal function in patients. On the other hand, our results are confirmed by many previous studies [5,7,8,35,36] who showed similar results.

The protective effect of captopril may be mediated by the elimination of local vasoconstriction that appear to be primarily responsible for the decrease in glomerular filtration [37]. It may be also due to increase of kidney GSH content that is observed in our study and confirmed by the findings of Andreoli [38] who showed that captopril because of its sulfhydryl group can scavenge H2O2 and can slightly reduce but doesn't eliminate oxidant induced cell injury.

Another explanation of captopril protective effect would be the inhibition of the endogenous angiotensinII formation in the kidney which constricts efferent arterioles thus contributing to the maintenance of glomerular capillary pressure and glomerular filtration [39,40]. Angiotensin II also considered a growth factor that plays an important role in the progression of kidney damage [41]. It can also induce synthesis of several mediators e.g.-α and IL-6 ,monocyte chemotactic protein and the activity of transcription factor NF-κB associated with the

presence of glomerular and interstitial inflammatory cells in the kidney [41,43] AngiotensinII blockade by captopril causes significant improvement of renal function after gentamicin induced renal injury in rats .

Results of the present investigation also showed that nifedipine, calcium channel blocker, exerted a protective effect against gentamicin induced nephrotoxicity better than captopril. This is evidenced by reduction of both serum urea and creatinine levels and renal MDA content .Nifedipine increased serum Na+ and Ca+2 levels and kidney GSH content.

However, slight improvement of structural changes was only observed. These results are confirmed by the findings of Homes et al.,[44] that nifedipine could protect against filtration failure in glycerol induced ARF .Zima et al.,[45] and Papanikolao et al.,[46] showed similar protection against cyclosporine induced renal failure. The increase in calcium observed in our study was confirmed by the observations of Elliot and Patchin [47] that nifedipine decreases calcium uptake by renal tubular epithelial cells thus elevates serum calcium levels.

The protective effect of nifedipine could be explained depending on the fact that nifedipine reduces calcium transfer across membranes and/or inhibiting the action of vasoconstrictive hormones [48].Nifedipine could also reduced oxidative stress and increased endothelial NO release [20] This is confirmed by the reduction of MDA and the increase in reduced GSH in renal tissue observed in our study.

Our study clearly demonstrated that the administration of nifedipine/captopril combination exacerbated gentamicin induced nephrotoxicity .This is indicated by the increase in mortality rate (70%) and the sever reduction in body weight. Serum urea, creatinine and renal MDA were highly elevated. The combination decreased sodium levels and increased serum calcium levels. In addition histopathological examination revealed the presence of necrosis in all nephron segments .These severe changes were not expected as previous studies showed that nifedipine/captopril combination have marked additive effect on blood pressure [49].Stornello et al [50] found that both drugs exerted additive effect on blood pressure and rennin and that captopril counteract heart rate increase caused by nifedipine. Furthermore Guazzi et al.,[51] showed that this combination did not change serum urea and creatinine levels. But all these studies are performed in human and in the absence of gentamicin intervention.

Our results suggested that captopril potentiated the calcium blocking activity of nifedipine as evidenced by the increase in serum calcium levels more than nifedipine alone and previous studies showed that calcium may augment oxidant induced injury.

It seems also that nifedipine mutually potentiated the effect of captopril on aldosterone system thus decreased sodium levels. The combination increased lipid peroxidation thus exacerbate the structural damage caused by gentamicin.However the exact mechanism underlying this deleterious effect of the combination and the nature of interaction need further investigation.

In summary, this study indicated that captopril and nifedipine each alone exerted protective effect against gentamicin induced nephrotoxicity, Nifedipine has better protective effect than captopril. However their combination potentiated gentamicin nephrotoxicity, to a serious extent. So it is recommended to avoid this combination along with gentamicin and to strictly follow up the patient if this combination is given to patients with renal impairment.

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تقييم تأثير الكابتوبريل و النيفيدايبين منفردين أو مجتمعين على التسمم الكلوي المستحدث في الجرذان بالجنتاميسن

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يستعمل عقار الجنتاميسين كمضاد حيوى لعلاج العدوى الخطيرة بالبكتيريا سالبة الجرام و لكن يبقى استعماله محدودا نظرا لإحدائه التسمم الكلوي وقد أظهرت الدراسات السابقة الدور المهم لنظام الرينين-انجيوتنسين في آلية الإصابة الكلوية.كما وجد إن غالقات قناة الكالسيوم (التي قد تستعمل مع مثبطات الإنزيم المحول للانجيوتنسين في علاج الأمراض التي تصيب الجهاز القلبي الوعائى) توثر على وظيفة الكلية.

استهدفت هذه الدراسة تقييم تأثير كل من عقار الكابتوبريل والنيفيدايبين على حدة أو مجتمعين على التسمم الكلوي المستحدث بالجنتاميسن.

تم تجريع الجرذان عن طريق الفم عقار الكابتوبريل بجرعة(٢٥مجم/كجم) والنيفيدايبين(٢٠مجم/كجم) كل حدة أو مجتمعين لمدة ٦ أيام قبل حقن الجنتاميسن٨٠مجم/كجم(داخل الغشاء البريتونى) و لمدة ٧ أيام إثناء حقن الجنتاميسن.و في نهاية المدة تم وزن جميع الجرذان ثم وزن إحدى الكليتين لكل حيوان بعد تشريحه كما تم تعيين المؤشرات الكيميائية الحيوية فى مصل الدم مثل الكرياتينين واليوريا الالبيومين و إنزيم الكتات دي هيدروجيناس و مستوى الصوديوم والكالسيوم.و عين المالونداياالدهيد كمؤشر لتأكسد الدهون في الكلية وكذلك المحتوى الكلوي من الجلوتاثيون المختزل. كما فحصت انسجة الكلى بالمجهر الضوئى.

وقد أشارت النتائج إلى أن الجنتاميسن قد أحدث زيادة معنوية في وزن الكلية وفى مستوى كل من الكرياتينين واليوريا و إنزيم الكتات دي هيدروجيناس وكذلك مستوى المالونداياالدهيد في الكلية ولكنه أدى إلى انخفاض مستوى الصوديوم والمحتوى الكلوي من الجلوتاثيون المختزل. مع حدوث تلف.في أنسجة الكلى.

كما دلت النتائج على أن الكابتوبريل قد أحدث انخفاضا معنويا في مستوى الكرياتينين و زيادة معنوية في المحتوى الكلوي من الجلوتاثيون المختزل كما انقص من حدة التلف المحدث في الأنسجة كما اتضح من النتائج أن النيفيدايبين قد ادى الى زيادة معنوية فى الكرياتينين واليوريا وكذلك مستوي المالونداياالدهيد في الكلية كما أحدث زيادة معنوية في مستوى الصوديوم والكالسيوم في مصل الدم وفى المحتوى الكلوي من الجلوتاثيون المختزل مع خفض حدة التلف المحدث فى الانسجة.

على العكس من ذلك أدى استخدام ا العقارين مجتمعين الى ارتفاع مستويات الكرياتينين واليوريا والكالسيوم في مصل الدم وكذلك مستوى المالونداياالدهيد في الكلية وانخفاض مستوى الصوديوم في مصل الدم يضاف الى ذلك احداثهما تلفا شديدا في جميع الأنسجة الكلوية.

مما سبق يتبين أن التعاطى المنفرد للكابتوبريل أوالنيفيدايبين له تأثير وقائي من التسمم الكلوي التجريبى المستحدث بالجنتاميسن. وقد ابدى النيفيدايبين نتائج أفضل من الكابتوبريل. بينما أدى استخدام العقارين معا إلى تفاقم هذا التسمم.