The effect of angiotensin receptor blocker on kidney functions in nephrotoxic rats

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Abstract

Gentamicin (GM) is one of the aminoglycosides antibiotics, it is effective drug in severe infections caused by Gram-negative bacteria. The major complication of GM is nephrotoxicity. Renin and angiotensin enzymes play important role in physiology of kidney, disturbance in this vasoconstrictor system is one of nephrotoxicity pathway. Several studies suggested that renin angiotensin system inhibitors show improvement in drug- induced nephropathies. This study was aimed to assess the effects of angiotensin receptor blocker losartan on renal functions in nephrotoxic rats. A number of male adult Sprague-Dawley rats 40 were used. They were divided into four groups (10 rats in each group). First group (I) was injected with 0.9% NaCl and regarded as a control, the second group (II) was injected with gentamicin intraperitoneally (IP) 100 mg/kg for 7 days. The third group (III) was pretreated with losartan orally (25 mg/Kg) for 10 days, then injected IP by gentamicin for other 7 days, while fourth group (IV) was treated with gentamicin and losartan (same doses) simultaneously for 7 days. The results indicated that gentamicin causes nephrotoxicity by increasing plasma creatinine (Pcr) and blood urea nitrogen (BUN) significantly. Oral administration of losartan for 7 days concurrently with gentamicin showed statistically significant improvement in kidney functions. However, pretreatment with losartan did not show significant protective effects. The study demonstrated that losartan can provide partial protection against gentamicin induced nephrotoxicity only when administered simultaneously with gentamicin.

Key words: Gentamicin, Losartan, Nephrotoxicity.

تأثير ألأدوية الغالقة لمستقبلات الأنجيوتنسين على وظائف الكلية في الجرذان المصابة بفشل كلوي

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الكلمات المفتاحية: لوسارتان جنتامايسين الفشل الكلوي

الخلاصة

ان دواء الجنتامايسين هو مضاد حيوي من مجموعة ال aminoglycosides وهو فعال لمعالجة الأمراض الخطيرة التي تسببها البكترية السالبة الصبغة ال Gram negative ومن اخطر المضاعفات التي يسببها هو تأثيره على عمل الكلية. ان انزيم الرنين والأنجيوتنسين لهما أهمية في الوظيفة الطبيعية للكلية وأن احدى الطرق

التي قد تؤدي الى الفشل الكلوي هو التغيرات التى تحدث لهذه الأنزيمات. هناك عدد من الدراسات اقترحت ان غلق المستقبلات التي تعمل عليها هذه الأنزيمات تحدث تحسنا في وظاف الكلية للمصابين بالفشل كلوي المستحدث بطرق مختلفة في الحيوانات التجريبية.أجريت هذه الدراسة لتقييم تأثير عقاراللوسارتان losartan (الذي يغلق مستقبلات الأنجيوتنسين) على وظائف الكلية في الجرذان بعد استحداث الفشل الكلوي فيها بأستخدام عقار الجنتامايسين .شملت الدراسة عدد 40 من الجرذان (ذكر بالغ) وزعوا عشوائيا الى اربعة مجاميع كل مجموعة مكونة من 10 جرذان. المجموعة الأولى تم زرقها بمحلول ملحي 0.9% NaClوأعتبرت مجموعة سيطرة, المجموعة الثانية تم زرقها داخل الغشاء البريتوني ب 100 ملغم/ كغم من الجنتامايسين لمدة سبعة أيام, المجموعة الثالثة تم اعطاؤها لوسارتان عن طريق الفم بجرعة 25 ملغم/كغم لمدة عشرة أيام ثم زرقت بالجنتامايسين لمدة سبعة أيام اخرى(نفس الجرعة السابقة), أما المجموعة الرابعة فقد تم اعطاؤها اللوسارتان وحقن الجنتامايسن في نفس الوقت لمدة سبعة أيام(نفس الجرع السابقة).أظهرت النتائج بعد اجراء التحليلات المختبرية في نهاية التجربة بقياس مستوى اليوريا والكرياتنين في الدم بان اللوسارتان يظهر تحسن ذات دلالة احصائية في وظائف الكلية عند اعطاؤه بالتزامن مع الجنتامايسين بينما لم يثبت اي تحسن عند اعطاؤه قبل زرق الجنتامايسين. أن نتائج الدراسة تثبت أن اعطاء عقار اللوسارتان قد يعطي حماية جزئية من التأثير السمي للجنتامايسين وذلك بتحسن وظائف الكلية المتمثلة بقياس اليوريا والكرياتنين فقط عند اعطاؤه بالتزامن مع المضاد الحيوي الجنتامايسين.

Introduction:

Gentamicin (GM) is one of the aminoglycosides antibiotics, it is effective drug in severe infections caused by serious Gram-negative bacteria. The major adverse effect and complication of GM is nephrotoxicity, more than 20% of patients taking gentamicin for one week shows this condition [1],. It has been reported that the mechanism of this complication is due to its high concentration in the renal proximal tubule that leads to direct tubular necrosis [2]. Free radicals and oxidative stress may have a role in this effect due to its accumulation in the renal cells as registered by other studies [3]. Release of vasoconstrictor mediators as a result of activation the renin-angiotensin system (RAS) has major role in renal necrosis [4]. Drug therapy in renal failure have two goals, either prevent or reverse the injury before its establishment[5] Renin - angiotensin system is important in normal physiology of kidney. Disturbances in this system is one of the renal failure pathways. Inhibition of RAS activity by using different drugs with different mechanism of actions reveals the improvement in kidney functions and histopathological changes in drug- induced nephrotoxicity [6].Angiotensin II receptor blockers(ARBs) have revealed better protective effect than renin angiotensin converting enzyme inhibitors (ACEIs) in kidney failure induced by cisplatin .ARBs have complex and different mechanisms in renoprotective effects, their effect as vasodilators reduce blood pressure and this may contribute to their renal protection in kidney failure[7]. Losartan is angiotensin II receptor blocker that has high affinity for AT1, it is used mainly for hypertension treatment, several studies indicated that it plays a chief role in reducing angiotensin -induced effects and improving kidney functions [8]. It was also evidenced to have protective effect against cisplatin and GM- treated rats. [9]. The renal vasodilation induced by ARBs causes increase in renal blood flow and improve ischemia and hypoxia that lead to renal injury, they also have effect on glomerular cells [10]. Several studies revealed effectiveness of different agents such as verapamil, saline loading, and captopril in protection the kidney from injury that induced by nephrotoxic substance, this indicates the possibility of involving more than

one pathophysiological mechanism in this type of injury and the complex mechanism by which this group of drugs ameliorate the renal injury [7.8].

Objective of study:

This study aimed to evaluate the effect of one members of angiotensin receptor blockers drugs (losartan) in kidney failure induced by gentamicin antibiotic in rats. The effect was evaluated when administered before and concurrently with gentamicin.

Method

Animals

Forty male albino rats, each one has weight of (180-200) gm was housed in cages and they were adapted for one week, then divided into four groups. Rats are drinking water and have their food normally all over the period of this study. The rats were injected with gentamicin in a one single dose of 100 mg/kg intraperitoneal (IP) for 7 days. Ampoule contains gentamicin 80 mg/2ml (Megental Menarini International; Italy) was used, the dose was given to the rats according to the body weight.

Study design

First group I (control group): Rats received NaCl (0.9%) intraperitoneally (IP) in volume that equal to gentamicin treated rats for 8 days.

Second group II (gentamicin group): Rats received gentamicin injection in a dose of 100 mg/kg IP once daily for 7 days to induce nephrotoxicity.

Third group III (pretreated with losartan): Rats received losartan 25 mg/kg/day orally by gastric tube for 10 days, then injected with gentamicin IP 100 mg/kg for 7 days

Forth group IV (losartan and gentamicin group): Rats administered losartan 25mg/kg orally concomitant with gentamicin injections (100 mg/kg)/day IP for 7 days. (Losartan was used as tablets50 mg, Amriya Comp).

Blood sampling was performed by cutting the tip of animal tail after injection of heparin subcutaneously and stored in labelled tubes.

Statistical analysis:

Results were demonstrated in a table and figure by using SPSS version 24. The differences between groups were also analyzed by using one -way ANOVA test. The level of significance was regarded when $p < 0.05$.

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Results:

The effects of losartan, gentamicin and their co-administration to rats on BUN and Pcr are summarized in table 1 and illustrated in figure 1.

The results recorded that BUN and Pcr were significantly higher than normal level in the 7^{th} day of GM administration (BUN 70± 5.5) (Pcr 2.5 ±0.8). when compared to the control group BUN (29 ± 4.2), (Pcr 0.8±0.55).

Concurrent treatment of losartan in (group IV) with gentamicin significantly reduced BUN and Pcr levels (BUN 35±6.4, Pcr 1.4± 0.45) that elevated by gentamicin alone, while the difference in BUN and Pcr levels were not statistically significant in the group that pretreated with losartan.

Table 1: Summary of blood urea nitrogen (BUN) and plasma creatinine (Pcr) values (mg/dl) during the period of the study

Treatments	BUN (mg/dl)	Pcr(mg/dl)
Group I	29 ± 4.2	0.8 ±0.55
Group II	70 ± 5.5 *	2.5± 0.8*
Group III	65 ± 4.8 Ns	2.8 ±0.4 Ns
Group IV	35 ±6.4 **	1.4±0.45 **

Group I= control, Group II= Gentamicin, Group III= Gentamicin + losartan pretreatment, Group IV= Gentamicin + losartan simultaneously

*= P < 0.05 Vs control ** = P < 0.01 Vs gentamicin, Ns = nonsignificant Vs Group II

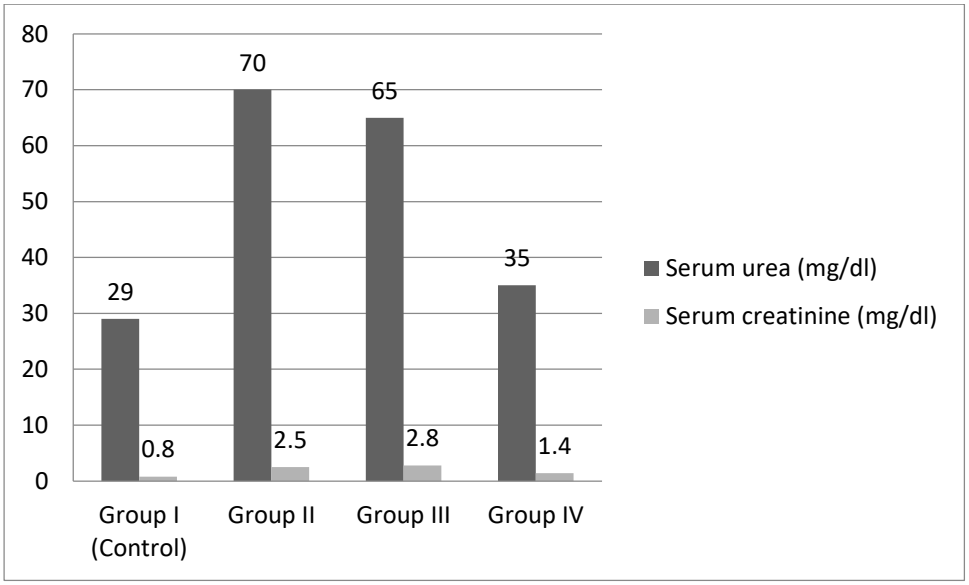

Figure 1: The effect of losartan and gentamycin on blood urea nitrogen and plasma creatinine in the four groups of the experimental rats.

Discussion

Gentamicin- induced nephrotoxicity has been reported by affecting renal functions and histopathological changes [11]. Gentamicin injected intraperitonially in a dose of 100 mg/ Kg for 7 successive days produced significant nephrotoxic effects and this evidenced by increase in BUN and Pcr, these results agree with previous studies using the same dose [12].

Different agents and drugs have been used to protect or reveres renal damage caused by GM such as extracts of garlic, turmeric, green tea, and sesame oil and stevia. Supplementation of vitamin C and E were also showed protective effect in GM- induced nephrotoxicity. The antioxidant properties of these different agents may have a role in renoprotection [13,14]. Calcium channel blockers, nifedipine and amlodipine were also suggested to have protective effects against GM nephrotoxicity [15]. They may protect the renal vessels to ischemia acute renal failure which was caused due to a change in smooth muscle Ca and endothelial derived relaxing factor EDRF [16,17].

Angiotensin was proposed to have a role in gentamicin nephrotoxicity, studies found that Angiotensin II has ability to produce free radicals such as superoxide in the kidney, and smooth muscles of the vessels [18]. Based on these information, Angiotensin II

blocker drugs (losartan and irbesartan) were evaluated for their renoprotective effects in gentamicin induced nephrotoxicity rodents' models [19,20]. In addition to effects of free radicals in kidney injury, high concentration of intracellular calcium induced by nephrotoxic agents also lead to formation of vasoconstrictor substances that cause renal dysfunction [15].

In this study, treatment with losartan concurrently with gentamicin significantly lowered BUN and Pcr, these findings are consistent with previous studies using cyclosporin, cisplatin, and gentamicin antibiotic [10,21].

The mechanism of this partial protection effects of losartan may be due to its antioxidant properties and its effect on AT1 receptors that reduces the production of free radicals [22]. Another study has shown that losartan with MgSO4 can provide marked protective effect against kidney failure caused by aminoglycosides, the possible mechanisms involved is inhibition of damaging caused by lipid peroxidation when they affect the levels of malondialdehyde (MDA) in kidney. The oxidative stress is also found to be reduced when used losartan by affecting the biomarkers induced by gentamicin [23].The national guidelines have recommended the use of ARBs in hypertensive patients with chronic renal disease, the possible mechanisms for this responsible for protective effects may be due to their hemodynamic effects or direct effects on renal cells[24].

Conclusion

According to present results, losartan reduced the level of biochemical variables blood urea nitrogen and plasma creatinine in the rats that administered gentamicin to the normal level, this indicates that it may protect the kidney from damaging as a result of using aminoglycosides antibiotics, but its beneficial effect is only obvious when administered simultaneously with gentamicin**.**

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