

Comparison of the effect of losartan versus candasartan on uric acid levels in hypertensive patients

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ABSTRACT

Background: It have been suggested by some studies that uric acid plays a causal role in the development of cardiovascular disease where as other studies concluded that uric acid merely reflects other concomitant risk factors, such as hypertension, insulin resistance, obesity, or lipid abnormality . Sartan drugs or angiotensin II receptor blockers do appear to lower uric acid levels (SUA). The clinical importance of this finding to patients with hypertension, or gout, or both is not yet known. The present study was aimed to compare the effects of the antihypertensive drugs losartan and candasartan on blood pressure and uric acid level in hypertensive patients.

Materials and Methods: A total of 80 newly diagnosed hypertensive patients were divided into two groups, with 40 patients in each group. Group 1 was given losartan (50 mg/day) and group 2 was given candasartan (8mg/day). A control group of 50 apparently healthy individuals was included. Blood pressure and uric acid were measured for controls and patients before and after drug administration.

Results: A significant increase in blood pressure and uric acid were found in hypertensive patients before starting treatment ($P < 0.001$), as compared with controls. After 2 months of treatment, the systolic and diastolic BP were significantly reduced in the both losartan and candasartan groups ($P < 0.001$). Both drugs were similarly effective in reducing the blood pressure in patients with hypertension with no statistical significant difference between the two treatments. Serum uric acid levels were only significantly reduced after 2 months of treatment with losartan ($P < 0.001$) but not with candasartan.

Conclusions: Our findings suggest that both losartan and candasartan therapy were similarly effective in reducing blood pressure in patients with hypertension. Losartan, but not candasartan, was associated with a significant reduction in serum uric acid levels. Our findings suggest that the losartan is the drug of choice in patients with hypertension and hyperuricemia and gout.

Key Words: Hypertension, hyperuricemia, losartan, candasartan.

الخلاصة:

المقدمة: اقترحت بعض الدراسات ان الحامض البولي يلعب دورا مهما في حدوث الامراض القلبية الوعائية. ان دور ادوية السارتانس او مثبطات الانجيوتنسين من النوع الثاني في انخفاض مستوى الحامض البولي لم يعرف بعد. وان الاهمية السريرية لهذا الاستنتاج لدى مرضى ارتفاع ضغط الدم والذين لديهم ارتفاع في مستوى الحامض البولي في الدم او داء النقرس لم يعرف بعد. ان الهدف من الدراسة الحالية هو لمقارنة تأثيرات اثنين من الادوية الخافضة للضغط والمعروفة جيدا اللوسارتان والكانداسارتان على مستوى الحامض البولي في مصل الدم لدى مرضى ارتفاع ضغط الدم.

المواد وطرائق العمل: أجريت هذه الدراسة على 80 مريضا شخوصا حديثا إصابتهم بالضغط العالي من النوع الخفيف. قسمت مجموعة المرضى إلى مجموعتين متكونة من 40 مريضا في كل مجموعة. أعطيت المجموعة 1 عقار اللوسارتان (50 ملغ / يوم) وأعطيت المجموعة 2 عقار الكانداسارتان (8ملغ / يوم). استغرقت فترة العلاج مدة

شهرين. تم اختيار 50 شخصا سليما من المتطوعين (يبدون أصحاء) طبيعى الضغط ليكونوا مجموعة الضبط. تم قياس ضغط الدم ومستوى الحامض البولي في مصل الدم لمجموعة الضبط والمرضى قبل وبعد العلاج. **النتائج:** وجدت النتائج ارتفاعا معنويا ملحوظا في ضغط الدم ومستوى الحامض البولي في مصل الدم لدى مرضى ارتفاع ضغط الدم بالمقارنة مع مجموعة الضبط. كما وجدت ايضا بعد شهرين من العلاج انخفاضا معنويا ملحوظا في ضغط الدم الانقباضي والانبساطي عند مجموعة اللوسارتان والكانداسارتان مع عدم وجود فرق معنوي بين عقاري اللوسارتان والكانداسارتان في علاج ارتفاع ضغط الدم. ولوحظ ايضا انخفاضا معنويا ملحوظا في مستوى الحامض البولي بعد المعالجة بعقار اللوسارتان فقط ولكن ليس مع عقار الكانداسارتان. **الاستنتاجات:** أظهرت هذه الدراسة أن هناك ارتفاعا معنويا ملحوظا في مستوى الحامض البولي في مصل الدم لدى مرضى ارتفاع ضغط الدم. أدى العلاج بعقار اللوسارتان لكن ليس العلاج بعقار الكانداسارتان إلى انخفاضا معنويا ملحوظا في مستوى الحامض البولي في مصل الدم يمكن أن يكون اللوسارتان علاجاً مفيداً للسيطرة على ضغط الدم وتقليل مستوى الحامض البولي في مصل الدم لدى مرضى ارتفاع ضغط الدم ولديهم فرط الحامض البولي في الدم وداء النقرس. **الكلمات المفتاحية:** ارتفاع ضغط الدم، فرط الحامض البولي بالدم، اللوسارتان، الكانداسارتان.

It have been suggested by some studies that uric acid plays a causal role in the development of cardiovascular disease¹ where as other studies concluded that uric acid merely reflects other concomitant risk factors, such as hypertension, insulin resistance, obesity, or lipid abnormality^{2,3}. Many drugs have hypouricemic properties, in addition to their main therapeutic effects. The oral weight loss agent sibutramine decreases serum uric acid in obese patients by 20% to 25%⁴. Similarly, in patients with type 2 diabetes and hyperuricemia, the insulin sensitizing agent troglitazone lowers serum uric acid by 20% to 25%⁵. Ramipril was found to increase the excretion of uric acid in a number of hypertensive patients⁶. There is observational data suggesting that sartans or angiotensin II receptor blocker (ARB), may affects SUA level⁷. The effects of the antihypertensive drugs, sartans, on serum uric acid level (SUA) is not well studied. The present study was conducted to compare the effects of losartan and candasartan on uric acid levels in hypertensive patients.

Patients And Methods

A total of eighty newly diagnosed patients with mild hypertension (Blood

pressure $\geq 140/90$ mmHg)⁸, were participated in this study. They were selected from the out-patient clinic in IBN-SINA teaching hospital in Mosul city. The study protocol was approved by regional Research Ethics Committees at the College of Pharmacy and Mosul Health Administration. The study was an open, controlled, comparative, clinical trial of two months duration.

The patients were divided into two groups each of 40 patients. Group 1 was given losartan 50 mg orally once daily for 2 months (Angizar[®] 50 mg, Micro pharmaceutical industries, Co. Ltd., India). They were 14 males and 26 females, with a mean age of 55.42 ± 7.97 years. Group 2 received candasartan 8 mg orally once daily oral dose for 2 months (Atacand[®] 8mg, AstraZeneca pharmaceutical industries, Co. Ltd., Sweden). They were 19 males and 21 females with mean ages of 54.22 ± 6.45 years. Another 50 healthy individuals matched in age and gender with study patients also participated in the study as a control group. They were 27 males and 23 females in this group with mean age of 53.4 ± 9.15 years.

Those with hepatic or renal diseases, pregnancy and lactation, and hypertensive patients on

antihypertensive therapy were excluded. Blood pressure was measured at baseline by standard mercury sphygmomanometer and at the end of 2 months treatment period with losartan or candasartan. Goal blood pressure after treatment was less than 140/90 mmHg. Serum uric acid was measured before and after losartan or candasartan administration by standard commercial kits by using a kit supplied from Biolabo (France)⁹.

All values are quoted as the mean \pm SD. Paired t-test was used to compare blood pressure and serum uric acid concentrations at baseline and after treatment. Unpaired t-test was used to compare serum uric acid concentrations between control and patient groups and between losartan and candasartan groups. The statistical results were considered significant at $p \leq 0.05$ ¹⁰.

Results

The systolic blood pressure (SBP) and diastolic blood pressure (DBP) were significantly higher ($p < 0.001$) in hypertensive patients before starting therapy with either losartan or candasartan in comparison with the control group (Table 1 and 3, respectively). After 2 months, the systolic and diastolic blood pressure were reduced in the losartan group from

151.2 \pm 7.72 to 138.0 \pm 7.14 mmHg and from 89.3 \pm 6.21 to 80.2 \pm 5.84 mmHg respectively, ($P < 0.001$) (Table 2), and in the candasartan group from 140.78 \pm 5.93 mmHg at baseline to 125.47 \pm 8.28 mmHg, and from 91.44 \pm 6.15 to 82.08 \pm 5.23 mmHg respectively, ($P < 0.001$) (Table 4). It has been found that losartan was as effective as candasartan in lowering systolic and diastolic blood pressure, (Table 5).

Baseline uric acid levels were 297.70 \pm 61.69 μ mol/l for losartan group and 300.86 \pm 54.70 μ mol/l for candasartan group which showed a significant elevation ($P < 0.001$) as compared with the control (280.87 \pm 66.52 μ mol/l) (Table 1 and 3, respectively). Comparison of uric acid levels before and after 2 months of therapy by each drug showed a significant reduction in losartan group (288.42 \pm 40.63 μ mol/l) ($P < 0.001$) (Table 2) and a non significant increase in the candasartan group (305.65 \pm 52.31 μ mol/l) ($p = 0.324$) (Table 4). Comparison of uric acid levels between losartan group and candasartan group showed a significant reduction in the SUA levels in the losartan group (-9.28 \pm 1.06 μ mol/l, $P < 0.001$) as compared with the candasartan group (4.79 \pm 9.86) (Table 5).

Table 1. Comparison of blood pressure and uric acid between control and losartan group

Parameter	Mean \pm SD		
	Control (n=50)	Before Drug (n=40)	After Drug (n=40)
SBP (mm Hg)	129.05 \pm 6.93	151.2 \pm 7.72***	138.0 \pm 7.14
DBP (mm Hg)	78.32 \pm 4.91	89.3 to \pm 6.21***	80.2 \pm 5.84
Uric acid (μ mol/l)	280.87 \pm 66.52	297.70 \pm 61.69***	288.42 \pm 40.63*

* Significant difference from control at $p < 0.05$ and *** at $p < 0.001$ using unpaired t-test

Table 2. The effect of losartan on blood pressure and uric acid

Parameter	Mean±SD		
	Before	After	p-value
SBP(mm Hg)	151.2 ±7.72	138.0±7.14	<0.001
DBP(mm Hg)	89.3 to ±6.21	80.2 ±5.84	<0.001
Uric acid (µmol/l)	297.70±61.69	288.42±40.63	<0.001

Using paired t- test (n=40).

Table 3. Comparison of blood pressure and uric acid between control and candasartan group

Parameter	Mean±SD		
	Control (n=50)	Before Drug (n=40)	After Drug (n=40)
SBP(mm Hg)	129.05±6.93	140.78±5.93***	125.47±8.28
DBP(mm Hg)	78.32±4.91	91.44±6.15***	82.08±5.23
Uric acid (µmol/l)	280.87±66.52	300.86±54.70***	305.65±52.31***

***Significant difference from control at $p \leq 0.001$ using unpaired t- test.

Table 4. The effect of candasartan on blood pressure and uric acid

Parameter	Mean±SD		
	Before	After	p-value
SBP(mm Hg)	140.78±5.93	125.47±8.28	<0.001
DBP(mm Hg)	91.44±6.15	82.08±5.23	<0.001
Uric acid (µmol/l)	300.86±54.70	305.65±52.31	0.324(NS)

Using paired t- test (n=40). NS= Non significant

Table 5. Comparison of percent variation of the studied parameters after therapy with losartan or candasartan

Parameter	Mean±SD (%)		p-value
	Losartan (n=40)	Candasartan (n=40)	
SBP(mm Hg)	-13.20±0.58	-15.31±2.35	0.164(NS)
DBP(mm Hg)	-9.10±0.73	-9.36±0.92	0.241(NS)
Uric acid (µmol/l)	-9.28±1.06	4.79 ±9.86	<0.001

NS=Not significant using unpaired t-test

Negative sign means decrease.

Discussion

The present study demonstrates significantly higher serum uric acid levels in patients with hypertension in comparison with the control group. These results are in consistent with the results obtained from many studies which also demonstrate increased levels of uric acid in patients with hypertension¹¹. Several mechanisms were attributed to the increase of serum uric acid levels in patients with hypertension. The increase in serum uric acid in hypertension may be due to the decrease in renal blood flow that accompanies the hypertensive state, since a low renal blood flow will stimulate urate reabsorption¹². and results in microvascular disease¹³. Proximal tubular reabsorption of serum uric acid occurs by an active transport mechanism closely linked to or identical with the tubular reabsorption of sodium¹⁴. Another mechanism for the increased serum uric acid levels in hypertension is that hypertension is associated with increased oxidative stress¹⁵. Because uric acid is considered to be an effective antioxidant. The elevated serum uric acid levels encountered in individuals with hypertension may reflect a compensatory mechanism counteracting the increased oxidative stress associated with the hypertension¹⁶.

In the present study, only losartan causes a significant reduction of serum uric acid concentrations in patients with hypertension after 2 months of therapy. These data are compatible with previous findings that suggested that losartan have urate lowering properties and indicated that losartan have uricosuric effects. Many studies have demonstrated that the uricosuric effect of losartan was due to the parent compound and not to the

active metabolite EXP 3174 and that this effect is independent of angiotensin II receptor blockade and is due to unique biochemical properties of losartan^{17,18}. The hypouricemic effect of losartan may be due to that losartan target the urate anion exchange and diminish urate reabsorption in the proximal convoluted tubule; as a result, the urate excretion fraction is increased by 13%-30% and increases renal uric acid excretion¹⁹. This aspect of losartan therapy might have therapeutic advantages by reducing the risk of elevated uric acid in patient with hypertension, since elevated serum uric acid levels in patient with hypertension regarded as a risk factor for the development of cardiovascular diseases and may ameliorate hyperuricemia induced by other drugs²⁰.

The ARBs candesartan and valsartan did not affect the SUA level²¹. In a study of 1161 hypertensive patients, candesartan slightly but significantly increased the SUA level²². Data obtained from the present study showed that candasartan produce non significant effects on uric acid concentration in patients with hypertension. These finding were in consistent with results obtained by Manolis et al.,²². Rise in serum uric acid levels reported by Rayner et al.,²³ and Berni et al²⁴. Since losartan have a beneficial effects on blood pressure and serum uric acid concentration, it could be considered the antihypertensive drug of choice in patients with hypertension and hyperuricaemia or gout.

In conclusions, this study demonstrates that both losartan and candasartan therapy were similarly effective in reducing blood pressure in patients with mild hypertension. Losartan, but not candasartan, was associated with a reduction in serum uric acid levels. Therefore, our findings

suggest that losartan may be the drug of choice in patients with hypertension and hyperuricemia or gout.

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