The effects of the addition of losartan on uric acid metabolism in patients receiving indapamide

Spyros Nikas, Evangellos Rizos, Haralampos Milionis, Eleni Bairaktari, Rigas Kalaitzidis, Kostas Siamopoulos and Moses Elisaf

Journal of Renin-Angiotensin-Aldosterone System 2000 1: 289
DOI: 10.3317/jraas.2000.045

Keywords:
losartan,
uric acid,
uricosuria,
hyperuricaemia

The effects of the addition of losartan on uric acid metabolism in patients receiving indapamide

Spyros Nikas, Evangellos Rizos, Haralampos Milionis, Eleni Bairaktari, Rigas Kalaitzidis, Kostas Siamopoulos, Moses Elisaf*

Department of Internal Medicine and Biochemistry Laboratory*, Medical School, University of Ioannina, Ioannina, Greece

Correspondence to:
Dr Moses Elisaf,
Associate Professor of Internal Medicine,
Department of Internal Medicine,
Medical School,
University of Ioannina,
451 10 Ioannina,
Greece
Tel: +30 651 97500
Fax: +30 651 45944
E-mail: melisaf@cc.uoi.gr

Accepted for publication
4th September 2000

JRAAS 2000;**1**:289-91

Abstract

Objective

A number of adverse metabolic effects are associated with indapamide administration, including an increase in serum uric acid levels. It has been reported that losartan can significantly decrease serum uric acid levels. However, there are no data on the effects of combination therapy of losartan with indapamide on uric acid metabolism.

Methods

We studied 20 hypertensive patients in whom serum metabolic parameters, including uric acid levels in serum and urine, were studied before and after eight weeks of indapamide administration (2.5 mg once daily) as well as eight weeks after combination treatment with indapamide (2.5 mg once daily) and losartan (50 mg/day).

Results

Indapamide evoked a significant decrease in systolic and diastolic blood pressure from a mean value of 157±12 mmHg/96±10 mmHg to a mean value of 139±14 mmHg/92±5 mmHg ($p<0.01$ for both comparisons). However, a significant increase in serum uric acid levels was noticed after indapamide administration (from a mean value of 4.9±1.6 mg/dl to a mean value of 5.9±1.2 mg/dl, $p<0.01$), associated with a decrease in the fractional excretion of uric acid (from a mean value of 9±5% to a mean value of 7±5.5%, $p<0.05$). The addition of losartan caused a further decrease in blood pressure from a mean value of 139±14 mmHg/92±5 mmHg to a mean value of 120±15 mmHg/84±4 mmHg ($p<0.01$ for both comparisons). This was followed by a significant decrease in serum uric acid levels to 5±1.1 mg/dl ($p<0.01$) due to a substantial increase in fractional urate excretion (from 7±5.5 to 8.7±6%, $p<0.05$).

Conclusion

The addition of losartan could offset the hyperuricaemic effect of indapamide administration.

Introduction

Indapamide is an effective and safe antihypertensive drug, which is thought to have minimal effects on lipids and glucose intolerance.[1,2] However, adverse metabolic effects, although to a lesser extent than the thiazides, including increased serum uric acid levels, have been reported after indapamide administration.[3] On the other hand, losartan, an angiotensin II (Ang II) receptor antagonist, can significantly decrease serum uric acid levels by augmenting uric acid excretion.[4,5] Furthermore, the rise in serum uric acid levels associated with the use of thiazide diuretics, was counterbalanced by the concomitant administration of 50 mg/day of losartan.[6,7] However, there are no data concerning the changes of uric acid metabolism after addition of losartan to patients on indapamide. Thus, we undertook the present study to evaluate the effects of the combination treatment with indapamide and losartan in non-diabetic hypertensive patients.

Table 1 Study population

Male	13
Female	7
Mean age, year (range)	44 (31–66)
Body weight (Kg)	69±9
Body mass index (Kg/m²)	27.2±2.6
Cigarette smokers	11

Material and methods

The study involved 20 adult patients with stage one untreated hypertension (blood pressure [BP] 140–159 mmHg/90–99 mmHg). Patients' characteristics relevant to the study are shown in Table 1.

All participants were followed-up as outpatients in the Lipid and Hypertension Clinic at our University Hospital. Each patient had normal hepatic and renal function tests, and none had any other significant disease or laboratory abnormality that may have compromised his or her safety by participation in this study. Additional exclusion criteria included (a) diabetes mellitus (fasting plasma glucose, >126 mg/dl); (b) history of myocardial infarction or unstable angina; (c) thyroid dysfunction (thyroid-stimulating hormone [TSH] levels, >5μU/ml at screening); (d) consumption of drugs that may influence BP values and uric acid levels, and (e) physical or psychosocial disorders that could interfere with protocol adherence.

Patients were instructed to follow a low-salt and high potassium diet to control BP and were admitted to the study if their BP was more than 140/90 mmHg after initial dietary counselling and lifestyle modification for ≥8 weeks. Patients were started on indapamide, 2.5 mg once daily, for four weeks. Since, at the end of this time, BP remained

Journal of the Renin-Angiotensin-Aldosterone System
(Including other peptidergic systems)

September 2000
Volume 1
Number 3

Table 2 Influence of indapamide and combination therapy on metabolic parameters

Parameters	Baseline	p[a]	After indapamide	p[b]	After combination therapy
Glucose (mg/dl)	92±12	0.05	103±9	NS	102±8
Insulin (mU/L)	8.7±4	0.05	14±7	NS	14±5
T CHOL (mg/dl)	230±22	0.05	247±18	NS	234±21
HDL CHOL (mg/dl)	55±11	NS	56±9	NS	56±8
LDL CHOL (mg/dl)	152±21	0.05	163±19	NS	155±18
TRG (mg/dl)	115±44	NS	123±52	NS	123±49
T CHOL/HDL CHOL	4.3±0.6	0.05	4.6±0.5	NS	4.45±0.55
Uric acid (mg/dl)	4.9±1.6	0.01	5.9±1.2	0.01	5±1.1
FE Uric acid (%)	9±5	0.05	7±5.5	0.05	8.7±6
Potassium (mmol/L)	4.6±0.4	0.05	4.1±0.5	NS	4.25±0.4
Magnesium (mmol/L)	0.82±0.06	0.05	0.77±0.07	NS	0.79±0.055
Phosphate (mg/dl)	3.05±0.8	NS	3.08±0.6	NS	3.22±0.5
Sodium (mmol/L)	143±3	NS	142±2	NS	141±2
Calcium (mg/dl)	9.6±0.6	NS	9.8±0.6	NS	9.8±0.5

Values expressed as mean±SD
T CHOL = total cholesterol; HDL CHOL = HDL cholesterol; LDL CHOL = LDL cholesterol; TRG = triglycerides; Apo = apolipoprotein; Lp(a) = lipoprotein (a); FE = fractional excretion.
[a]Compared with baseline values; [b]Compared with values obtained after indapamide therapy

To change glucose levels to mmol/L multiply by 0.055, to change insulin to pmol/L multiply by 7.18, to change cholesterol levels to mmol/L multiply by 0.02586, to change triglyceride levels to mmol/L multiply by 0.113, to change uric acid levels to µmol/L multiply by 59.5, to change phosphate levels to mmol/L multiply by 0.323, to change calcium levels to mmol/L multiply by 0.25.

above 140/90 mmHg in all cases, losartan, 50 mg once daily, was added for another four weeks.

At each visit, BP was measured and fasting (14-hour) blood samples were obtained for the determination of serum lipid parameters, (serum cholesterol, high-density lipoprotein [HDL] cholesterol, low-density lipoprotein [LDL] cholesterol and triglycerides), serum insulin, creatinine and uric acid levels and plasma glucose levels. A fresh urine specimen was also obtained within four hours after losartan administration for the measurement of creatinine, sodium, and uric acid levels.

Laboratory determinations

Commercially available techniques were used for the determination of serum and urine metabolic parameters, as previously described. Serum and uric acid levels were determined by a uricase / PAP method on Olympus AU 600 (Olympus Diagnostica, Hamburg). A standard formula was used for the determination of the fractional excretion (FE) of uric acid.

Statistical analysis

The results are expressed as mean±SD. Paired Student's *t*-test or Wilcoxon signed-ranks test was used for statistical analysis. Correlation coefficients were obtained by linear regression analysis or by the nonparametric Spearman rank test, where appropriate. Statistical significance was accepted at $p<0.05$.

Results

There was no significant change in mean body weight throughout the study, and every effort was made for the participants to sustain their dietary habits. Indapamide evoked a significant decrease in BP values from a mean value of 157±12 mmHg/96±10 mmHg to a mean value of 139±14 mmHg/92±5 mmHg ($p<0.01$ for both comparisons). However, drug treatment was followed by an increase in serum uric acid levels by 20.4% from a mean value of 4.9±1.6 mg/dl to a mean value of 5.9±1.2 mg/dl, associated with a significant decrease in the fractional excretion of uric acid by 22.2% from a mean value of 9±5% to 7±5.5%. There was a very good correlation between serum uric acid levels increase and the decrease in its fractional excretion ($r=0.62$, $p=0.01$). The addition of losartan caused a further decrease in BP values (from a mean value of 139±14 mmHg/92±5 mmHg to a mean value of 120±15 mmHg/84±4 mmHg $p<0.01$ for both comparisons) and resulted in a significant decrease in serum uric acid levels (by 15.2%) as a result of, at least in part, a significant increase (by 24.3%) in uric acid excretion. Thus, the addition of losartan could offset the indapamide-induced increase in serum uric acid levels, which at the end of the study reached the pre-treatment values. Again, the decrease in serum uric acid levels after losartan administration was inversely correlated with the increase in its fractional excretion ($r=-0.52$, $p=0.04$). As shown in Table 2, indapamide significantly decreased serum potassium and magnesium levels and increased serum total and LDL cholesterol as well as the atherogenic risk ratio total cholesterol/HDL cholesterol. Besides uric acid levels, the addition

of losartan did not significantly alter serum metabolic parameters.

Discussion

Our study showed that relatively high doses of indapamide (2.5 mg/day) could cause a number of adverse metabolic effects, including an increase in serum uric acid levels, which was mainly due to a significant decrease in the fractional urate excretion. Most diuretics are organic acids that may interfere with the secretion of uric acid into the proximal tubule.[8] However, this is not the sole or even the major mechanism of their effect on serum uric acid levels. The major effect seems to be mediated by volume depletion *per se* with accompanying increased proximal tubule reabsorption of uric acid.[8]

Previous studies have shown the uricosuric and hypouricaemic properties of losartan, which may be potentially important in treating hypertensive patients who commonly exhibit increased uric acid levels.[4,5] The possible beneficial influence of adding losartan to diuretics in order to offset their hypouricaemic effect has been examined in previous studies with contraversial results. It has been reported that the hypouricaemic effect of 25 mg of thiazide diuretic could be largely reversed, or at least somewhat blunted, by concomitant administration of 50 mg losartan.[6,7] However, in another study, Ruilope *et al.* showed that, in the losartan plus hydrochlorothiazide (25 mg/day) group, there was a slight increase in serum uric acid levels by 36 μmol/L.[9] Our study was the first to use indapamide instead of thiazides in this setting and to show clearly that the addition of losartan could completely offset the indapamide-induced increase in serum uric acid levels by enhancing the fractional urate excretion.

Inconsistent results have been described concerning the effect of losartan on uric acid excretion. Whereas some studies demonstrated a significant uricosuria with losartan,[5,10,11] others failed to do so.[12] However, experimental data clearly showed that the uricosuric activity of losartan is, at least in part, due to inhibition of urate reabsorption in the proximal tubule, is unrelated to Ang II-receptor activity, and is caused by the parent compound rather than the metabolite.[13] Furthermore, losartan has a greater affinity for the urate/anion exchanger than the other Ang II antagonists tested.[13] It should be mentioned that the uricosuric effect is transient and is observed mainly during the four to six hours after drug administration, which is why urine specimens were collected within four hours after losartan dosing in this study.[5,11] It has been reported that the losartan-induced uricosuria is not seen with other drugs of this class or with angiotensin converting enzyme inhibitors.[13-15]

Interestingly, this uricosuric effect of losartan is not associated with a significant increase in urinary dihydrogen urate, the primary risk factor for acute urate nephropathy, in hypertensive patients with thiazide-induced hyperuricaemia.[16] This could be due to a simultaneous drug-induced increase in urine pH so that the undissociated uric acid urine supersaturation (SS) fails to rise.[16] In fact, losartan has been shown to markedly reduce bicarbonate reabsorption in the proximal tubule, an effect which could be related to Ang II antagonism, since Ang II stimulates proximal tubule reabsorption of bicarbonate.[17] Thus, the lack of an increase in uric acid SS with losartan is a predictable consequence of the drug's effects on bicarbonate reabsorption.

Despite the fact that we cannot draw firm conclusions concerning the drugs' effects on BP values (our study was not double-blind, randomised, or cross-over), uric acid homeostasis changes were unlikely to be affected by the open protocol.

Our data have confirmed the mild uricosuric and hypouricaemic effect of losartan, whereas for the first time, it is shown that combination therapy with indapamide and losartan is not associated with any change in serum uric acid levels.

References

1. Osei K, Holland G, Falko M. Indapamide. Effects on apoprotein, lipoprotein, and glucoregulation in ambulatory diabetic patients. *Arch Intern Med* 1986; **146**: 1973-7.
2. Campell DB, Moore RA. The pharmacology and clinical pharmacology of indapamide. *Postgrad Med J* 1981; **57**(Suppl 2): 7-17.
3. Elisaf MS, Theodorou J, Pappas H *et al*. Effectiveness and metabolic effects of perindopril and diuretics combination in primary hypertension. *J Hum Hypertens* 1999; **13**: 787-91.
4. Elisaf M, Tsimichodimos V, Bairaktari E *et al*. Effect of micronized fenofibrate and losartan combination on uric acid metabolism in hypertensive patients with hyperuricemia. *J Cardiovasc Pharmacol* 1999; **34**: 339-46.
5. Nakashima M, Uematsu T, Kosuge K *et al*. Pilot study of the uricosuric effect of DuP-753: a new angiotensin II receptor antagonist, in healthy subjects. *Eur J Clin Pharmacol* 1992; **42**: 333-5.
6. Flaherty JT, Edelman J, Kivlighn S. Effects of a low dose of thiazide diuretic on serum uric acid: Comparison of a losartan–based regimen vs usual care. (Abstract) 71st Scientific Session AHA. *Circulation* 1999: I-723.
7. Soffer BA, Wright JT, Pratt JH *et al*. Effects of losartan on a background of hydrochlorothiazide in patients with hypertension. *Hypertension* 1995; **26**: 112-7.
8. Grantham IJ, Chanko AM. The physiological basis and clinical uses of diuretics. In Brenner BM, Steind, eds. Sodium and water homeostasis. New York: Churchill Livingstone 1978: 178-211.
9. Ruilope LM, Simpson RL, Toh J *et al*. Controlled trial of losartan given concomitantly with different doses of hydrochlorothiazide in hypertensive patients. *Blood Press* 1996; **5**: 32-40.
10. Tsunoda K, Abe K, Hagino T *et al*. Hypotensive effect of losartan, a nonpeptide angiotensin II receptor antagonist, in essential hypertension. *Am J Hypertens* 1993; **6**: 28-32.
11. Burnier M, Rutschmann B, Nussberger J *et al*. Salt-dependent renal effects of an angiotensin II antagonist in healthy subjects. *Hypertension* 1993; **22**: 339-47.
12. Grossman E, Peleg E, Carroll J *et al*. Hemodynamic and humoral effects of the angiotensin II antagonist losartan in essential hypertension. *Am J Hypertens* 1994; **7**: 1041-4.
13. Edwards RM, Trizna W, Stack EJ *et al*. Interaction of nonpeptide angiotensin II receptor with the urate transporter in rat renal brush-border membranes. *J Pharmacol Exp Ther* 1996; **276**: 125-9.
14. Burnier M, Roch-Ramel F, Brunner HR. Renal effects of angiotensin II receptor blockade in normotensive subjects. *Kidney Int* 1996; **49**: 1787-90.
15. Burnier M, Brunner HR. Angiotensin II receptor antagonists. *Lancet* 2000; **355**: 637-45.
16. Shahinfar S, Simpson RL, Carides AD *et al*. Safety of losartan in hypertensive patients with thiazide-induced hyperuricemia. *Kidney Int* 1999; **56**: 1879-85.
17. Cogan MG, Xie MH, Lin FX, Wong P, Timmermans PB. Effect of DuP 753 on proximal nephron and renal transport. *Am J Hypertens* 1991; **4**: 315S-3120S.