

Effect of hydrochlorothiazide with amiloride on serum lipid profile and malondialdehyde in hypertensive women

Faris A. Ahmed

Department of Physiology, Nineveh College of Medicine, University of Mosul.

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ABSTRACT

Objectives: To study the effect of hydrochlorothiazide with amiloride on serum lipid profile and malondialdehyde (MDA) in hypertensive women.

Methods: A case-control study was carried out in the Outpatient Department in Ibn-Sina General Hospital, Mosul, during the period from November 2005 to May 2006. Thirty hypertensive women treated with 50 mg hydrochlorothiazide and 5 mg amiloride per day in a single dose. The duration of treatment was between 1-5 years. Thirty mild hypertensive women (newly diagnosed, before treatment) were also included as a control group. Blood samples were taken from both the treated patients and controls and analysed for serum lipid profile and MDA. Non-paired 't'-test was used to compare between parameters.

Results: Hydrochlorothiazide with amiloride did not change serum lipid profile significantly in the hypertensive women compared with the control group, although serum lipid profile was in the upper normal value. The combination therapy decreased serum MDA significantly ($P < 0.05$).

Conclusion: Chronic use of combination therapy of hydrochlorothiazide with amiloride had no significant effect on serum lipid profile, but this combination reduced lipid peroxidation in hypertensive women. Lipid peroxidation is a consequence and not a cause of hypertension.

Keywords: Lipid profile, lipid peroxidation, malondialdehyde, hypertensive women.

الخلاصة

أهداف البحث: دراسة تأثير عقار هايديروكلوروثيازيد مع عقار اميلورايد على مصلى واجهة الدهون ومصل مالونداالدهايد **التصميم:** دراسة مقارنة للحالات العلاجية مع الحالات الضابطة.
مكان إجراء الدراسة: تمت الدراسة في العيادة الخارجية في مستشفى ابن سينا العام في الموصل للفترة من تشرين الثاني ٢٠٠٥ ولغاية أيار ٢٠٠٦.

طرائق العمل: أجريت الدراسة على ثلاثين امرأة مصابة بفرط الدم الشرياني وتحت علاج عقار هايديروكلوروثيازيد ٥٠ ملغم مع عقار اميلورايد ٥ ملغم في اليوم بجرعة واحدة. وكانت مدة العلاج من ١-٥ سنوات. وشملت الدراسة أيضا مجموعة سيطرة مكونة من ثلاثين امرأة مصابة بفرط الدم الشرياني المتوسط (مشخصة حديثا وبدون علاج). وأخذت عينات الدم من كلا المجموعتين للحصول على مصلى واجهة الدهون ومصل مالونداالدهايد. وتمت المقارنة بين المجموعتين باستعمال اختبار (ت).

النتائج: لم يغير عقار هايديروكلوروثيازيد مع عقار اميلورايد مصلى واجهة الدهون في النساء المصابات بفرط الدم الشرياني مقارنة بالمجموعة الضابطة، ولكن كان مستوى واجهة الدهون في مصلى الدم قد بلغ أعلى مستوياته الطبيعية. وقلل العلاج الترابطي من عقار هايديروكلوروثيازيد مع عقار اميلورايد معنويا ($P < 0,05$) مصلى مالونداالدهايد مقارنة مع المجموعة الضابطة.

الاستنتاج: إن الاستعمال المزمّن للعلاج التوافقي لعقار هايديروكلوروثايزايد مع عقار اميلورايد لم يؤثر معنويًا على واجهة الدهون في النساء المصابات بفرط الدم الشرياني لكن هذا العلاج التوافقي قلل معنويًا من زناخة الدهون. إن زناخة الدهون هي نتيجة وليست سبب ارتفاع ضغط الدم الشرياني.

Thiazides are moderately potent diuretics that increase urine flow, sodium and potassium excretion⁽¹⁾. Hydrochlorothiazide has important effect on hypertension as a single therapy⁽²⁾. However, no trials have been done for evaluating the efficacy of amiloride, the potassium sparing diuretic, as a blood pressure lowering monotherapy⁽³⁾. The combination of hydrochlorothiazide and amiloride is used for the treatment of hypertension and the rationale for combination is to spare potassium and magnesium loss through the kidney⁽⁴⁾.

Hydrochlorothiazide caused significant increase in serum triglycerides (TG)⁽⁵⁾. Moser⁽⁶⁾ found that the rate of dyslipidaemia was higher with thiazide diuretics than loop diuretics. However, these disturbances in lipid profile were negligible at half standard dose of thiazide diuretics⁽⁷⁾. The potassium sparing diuretic, spironolactone, exerted no relevant effect on lipid profile⁽⁸⁾. There is well defined relationship between thiazide and dyslipidaemia but not with spironolactone⁽⁹⁾.

Lipid peroxidation of cell membrane was associated with a number of pathological conditions including atherosclerosis and thrombosis⁽¹⁰⁾. Essential hypertension was also associated with increased oxidative stress and reduced antioxidant status⁽¹¹⁾. In addition, antihypertensive drugs and some diuretics exerted a positive effect on the imbalance between peroxide on lipid and antioxidant defense system⁽¹²⁾.

Usually, hydrochlorothiazide and amiloride are used in combination for the treatment of hypertension. Therefore, this study was conducted to evaluate the effect of this combination of drugs on serum lipid profile and lipid peroxidation presented by serum malondialdehyde (MDA).

Patients and methods

This study received approval from Nineveh Directorate of Health (Medical Research Ethical Committee, consents of patients were

taken for this study). The study was carried out in the Outpatient Department in Ibn Sina Teaching Hospital in Mosul, from November 2005 to May 2006. Two groups of 30 female patients for each group were studied (under supervision of cardiologist). Patients of the first group received 50 mg hydrochlorothiazide with 5 mg amiloride per day in a single dose. The age of the treated patients ranged between 43-74 years (mean±SD: 51.8±7.6 years). The duration of treatment was between 1-5 years. The second group included mild hypertensive patients (early diagnosed before treatment). Their ages ranged between 45-74 years (mean ± SD: 51.6±7.6 years). Patients with other diseases or receiving medication other than the studied drugs were excluded from this study.

Six ml of blood were collected from each patient, after overnight fasting. The sera were separated for the analysis of lipid profile and MDA. Determination of serum TC (total cholesterol), triglycerides (TG) and high density lipoprotein cholesterol (HDL-C) were performed by enzymatic methods⁽¹³⁻¹⁵⁾. Serum low density lipoprotein cholesterol (LDL-C) was calculated using Friedewald formula⁽¹⁶⁾. Serum MDA was estimated by the method of Buege and Aust⁽¹⁷⁾.

Data are presented by mean±SD and were analysed using unpaired t-test.

Results

In hypertensive patients treated with hydrochlorothiazide and amiloride, serum TC, TG, LDL-C, VLDL-C, HDL-C and ratio TC/HDL-C were not significantly different compared with the results in the non-treated patients (controls) (Table 1). However, values for serum lipid profile in the treated patients were in the upper normal limit based on the recommendation of British Hyperlipidaemia Association (1998)⁽¹⁸⁾.

Serum MDA was decreased significantly ($P<0.05$) in the treated patients compared with the non-treated patients (controls) (Table 1).

Table (1): Serum lipid profile and malondialdehyde in the control group and treated patients with hydrochlorothiazide and amiloride.

Hypertensive subjects	TC mmol/L	TG mmol/L	LDL-c mmol/L	VLDL-C mmol/L	HDL-C mmol/L	TC mmol/L	MDA μ mol/L
Controls N = 30	4.08 \pm 1.59	1.30 \pm 0.67	2.18 \pm 1.52	0.59 \pm 0.34	1.3 \pm 0.34	3.53 \pm 3.14	0.204 \pm 0.125
Treated patients N = 30	4.99 \pm 1.85	1.66 \pm 0.59	3.09 \pm 1.9	0.75 \pm 0.27	1.15 \pm 0.39	4.87 \pm 2.38	0.134* \pm 0.069

TC: total cholesterol; TG: triglycerides; LDL-c: low density lipoprotein cholesterol; VLDL-c: very low density lipoprotein cholesterol; MDA: malondialdehyde. *P<0.05.

Discussion

In this study hydrochlorothiazide and amiloride combination did not produce significant change in serum lipid profile in the patients. However, many studies showed that thiazides cause dyslipidaemia^(8,9). Hydrochlorothiazide increased serum TG and VLDL-C⁽¹⁹⁾. The effect of thiazides on lipids appears to be dose dependent, since higher dosage of hydrochlorothiazide increased serum TC and LDL-C⁽⁸⁾, whereas low dose of hydrochlorothiazide did not produce significant change in plasma lipid⁽²⁰⁾.

The duration of treatment, in this study, was more than one year which may explain the minimal alteration in lipid profile caused by the treatment. These results are consistent with other workers^(21,22).

There are several theories of dyslipidaemia induced by diuretics, one theory suggested that thiazide induced reduction in insulin sensitivity might cause an associated increase in hepatic production of cholesterol⁽²³⁾. This observation may be more related to the reduction in serum potassium occurred with high dose of thiazides⁽²⁴⁾. The absence of even short term negative lipid effect of low doses of thiazides may be due to decreased incidence of hypokalaemia and associated insulin resistance⁽²⁵⁾.

Accordingly, serum lipid profile did not change in the studied patients, since amiloride was used in the combination therapy to maintain potassium balance. In addition, amiloride did not increase blood levels of lipid⁽²⁶⁾. Also, there is well defined relationship

between thiazides and dyslipidaemia but not with spironolactone⁽⁹⁾.

The combination of diuretics, in the present patients, decreased lipid peroxidation presented by serum MDA. Many studies showed an increase in lipid peroxidation accompanied with antioxidant imbalance in hypertensive patients^(27,28). Antihypertensive therapy decreased both blood pressure and oxidative stress in hypertensive patients^(11,29). Therefore, lipid peroxidation is a consequence and not a cause of hypertension⁽²⁹⁾. However, the possibility that therapy targeted by decreasing generation of reactive oxygen species may be useful in minimizing vascular damage⁽³⁰⁾.

In conclusion, chronic treatment of hydrochlorothiazide with amiloride did not change lipid profile in hypertensive women, but this combination decreased lipid peroxidation. Lipid peroxidation is a consequence and not a cause of hypertension.

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