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PROTECTIVE EFFECTS OF PERINDOPRIL, AMLODIPINE, METOPROLOL AND INDAPAMIDE ON HYPERTENSION INDUCED LEFT VENTRICULAR HYPERTROPHY IN RENOVASCULAR HYPERTENSIVE RATS: BIOCHEMICAL AND HISTOPATHOLOGICAL STUDY

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ABSTRACT

The objective of this study was to evaluate the efficacy of 6 weeks daily oral administration of different classes of antihypertensive drugs in renovascular hypertensive adult male rats. The effects of angiotensin converting enzyme (ACE) inhibitors (perindopirl, 0.08 mg/kg), calcium channel blocker (amlodipine, 0.15 mg/kg), β-blocker (metoprolol, 0.005 mg/kg) and a diuretic (indapamide, 0.5 mg/kg) were studied on elevated blood pressure and hypertension induced left ventricular hypertrophy (LVH), the latter was measured as left ventricular wall thickness and left ventricular nuclear density. Also, the effect of the mentioned drugs on some metabolic variables such as lipid profile represented by serum cholesterol, triglyceride (TG) and high density lipoprotein (HDL) as well as on serum blood glucose and serum Na^+ and K^+ levels was examined. All of perindopril, amlodipine metoprolol and indapamide significnatly decreased the elevated blood pressure and protected against hypertension induced LVH, but non of these drugs could affect left ventricular nuclear density. Indapamide significantly reduced blood glucose level and serum Na^+ and K^+ levels, whereas, perindopril markedly elevated serum Na^+ level. Neither amlodipine nor indapamide could affect the lipid profile but perindopril benificially affected serum lipid profile by increasing HDL. Conversly, metoprolol increased cholesterol and TG and decreased HDL significantly. In conclusion, periondoproil in the present model (2 kidneys, one clip renovascular hypertensive rats) would seem to have some advantages over the other used antithypertensive drugs in terms of lowering the elevated blood pressure and protecting against hypertension induced LVH. It laso improved the lipid profile as it increased HDL and seemed to have neutral effect on blood glucose level.

INTRODUCTION

Today, diuretics, beta blockers, calcium antagonist and angiotensin converting enzyme (ACE) inhibitors are considered first line drugs in the treatment of hypertension. Patients whose blood pressure is inadequately controlled by one of these drugs are often transfered to a different class of antihypertensives, rather than receiving additional drugs[1]. Such switches may be promoted not only for improved efficacy, but also by the hope that particular properties of the new medication will lead to decreased side effects or other therapeutic goals[2].

The main risks associated with hypertension do not arise from the increased blood pressure itself, but rather from pathological changes in a number of key organs. The structural changes in the cardiovascular system occur secondary to hypertension are characterized by an increase in myocardial mass with resultant impaired compliance and myocardial function and an increase in blood vessels wall thickness[3], as well.

Animals data have shown that different classes of antihypertensive drugs differ markedly in their ability to prevent or reverse the remodelling process secondary to hypertension[4]. The ideal antihypertensive drugs must control blood pressure as well as reducing ventricular mass and other complications [5,6], with minimal side effects.

From these contexts, the present work was designed to study the effect of some recent antihypertensive drugs belonging to different classes; ACE inhibitors represented by perindopril, calcium antagonists represented by amlodipine, beta blockers as metoprolol and diuretics represented by indapamide. The effect of these drugs was recorded on blood pressure, blood glucose level, some electrolytes and lipid profile as well as their efficacy in preventing some cardiovascular complications namely LVH judged by measuring the left ventricular myocyte thickness and left ventricular nuclear density in adult male renal hypertensive rats.

MATERIAL AND METHODS

Thirty six adult male albino rats weighing 180-200g were used in the present study. The animals were allowed free acess of food and water and housed in plastic cages under standardized conditions away from any stressful stimuli.

Rats were initially divided into two groups (6 and 30 rats). The former group was kep as normotensive control while the latter group was subjected to induction of hypertension. Hypertension induced experimentally by two kidneys, one clip renal artery stenosis by appliation of silver clip (0.2 mm internal diameter) to the left renal artery according to the method described by Leenen and Dejong (1971)[7] and Douglas et al. (1978)[8].

The normotensive control group was subjected to Sham operation without introduction of silver clip. Animals of this group were used to measure normal blood pressure, base line biochemical parameters normal cardiac muscle thickness and nuclear density. In both groups blood pressure was measured in rats anaesthetized by I.P. injection of 35 mg/kg pentobarbitone via blood pressure transducer PT 400,

connected to an oscillograph 400 MD 2 C (Palmer, BioScience, Washington).

Rats of the other group were randomly subdivided into 5 subgroups (6 each). All rats received daily oral treatment doses for 6 weeks as follows:

subgp I, perinodopril (0.08 mg/kg),

subgp II amlodipine (0.15 mg/kg),

subgp III metoprolol (0.005 mg/kg),

subgp IV. Indapamide (0.5 mg/kg).

The last group received distilled water and was left for 6 weeks to develop hypertension and served as hypertensive control.

At the end of the experiment, animals were sacrificed and blood was collected in plastic vials which were kept in refregirator at -4°C. Sera were obtained for determination of serum blood glucose level[9], total cholesterol[10], triglycerides [11] and HDL [12]. Serum electrolytes (Na^+, K^+) were measured spectrophotometrically according to standard procedure induced in the assay kits. Assay kits were obtained from Guimica Aplicada SA, Spain.

The hearts were exised, weighed and fixed in 10% formalin solution. Each heart was cut perpendicularly from apex to base axis into 4 specimens of identical thickness. Paraffin sections were cut 3 µm thick and stained with Hx and E. Morphometry was done using (As 200 image analyser micrometer version (Elmhursl, IL).

To measure the left ventricular cardiac muscle thickness 10 randomly selected fields on each slide were analysed and the mean value was taken. Left ventricular nuclear density was measured by determining the number of myocyte nuclei in 10 randomly selected fields on each slide at magnification of X 40.

Statistical analysis:

Results are presented as means ±S.E. Statistical significance was determined by the Students t-test at $P<0.05$.

RESULTS

Effects of six weeks daily oral administration of perindopril (0.08 mg/kg) amlodipine (0.15 mg/kg) metoprolol (0.005 mg/kg) and indapamide (0.5 mg/kg) in control hypertensive rats:

1-Mean arterial blood pressure:

Administration of perindopril, amlodipine, metoprolol and indapamide significantly reduced, the mean arterial blood pressure of control hypertensive rats from 156±5.257 mmHg to 83.667±1.713, 95±4, 92.2±2.332 and 120.883±8.53 mmHg respectively (Fig. 1).

2-Left ventricular cardiac wall thickness:

The mean thickness of the left ventricular wall of the heart was significantly reduced after perindopril, amlodipine, metoprolol and indapamide from 15.28±0.25 µ of the hypertyensive control to 9618±0.307, 10.776±0.325, 12.336±0.372 and 11.738±0.499 respectively (Fig. 2).

3-Left ventricular nuclear density:

Non of the previously mentioned drugs could significantly affect the mean level of the nuclear density of the ventricle from that of the hypertensive control (Fig. 3).

4-Serum glucose level:

The concentration of serum glucose was significantly reduced from control value only after administration of indapamide from 72.19±1.669 mmol/dL to 61.617±3.131 mmol/dL after six weeks treatment (Fig. 4).

5-Serum cholesterol, TG and HDL levels:

The mean serum level of HDL of the hypertensive control was significantly elevated after perindopril administration from 28.167±1.798 mg/dL to 38.5±1.626 mg/dl. Metoprolol significantly reduced the level of the mean HDL of the control to 20.0±0.925 mg/dl and elevated the mean cholesterol and TG level to 101.833±2.015 mg/dL and 138.883±3.356 mmol/dL from that of the control value (75.33±3.287 and 90.429±6.423) Table 1.

Table (1): Effect of perindopril, amlodipine, metoprolol and indapamide on serum cholesterol, triglycerides (TG) and high density lipoprotein (HDL) levels in adult male renal hypertensive rats.

Treatment	Serum cholesterol level (mg/dL)	Serm TG levele (mmol/dL)	Serrum HDL level (mg/dL)
Control (hypertensive rats)	75.33±3.287	90.429±6.423	28.167±1.798
Perindopril (0.08 mg/kg)	73.661±6.309	86.000±8.866	38.500±1.626*
Amlodipine (0.15mg/kg)	72.167±7.161	85.667±7.467	29.833±1.753
Metoprolol (0.005mg/kg)	101.833±2.015*	138.833±3.356*	20.000±0.925*
Indapamide (0.5 mg/kg)	79.167±5.224	92.637±6.526	30.167±2.424

Data are presented as mean ±SE

* Significantly different from control value at $P<0.05$

6- Serum Na^+ and K^+ levels:

Serum Na^+ concentration was significantly elevated from 170.667±0.265 mmol/L to 199.896±2.154 mmol/L only after administration of perindopril. Indapamide significantly reduced serum K^+ level of the hypertensive control from 5.737±0.208 to 4.933±0.108 (Table 2).

Histopathological results:

Relative decrease in left ventricular wall thickness was observed after all antihypertensive drugs' treatment in comparison to the hypertensive control group Fig. (5, 6, 7).

Table (2): Effect of perindopril, amlodipine, metoprolol and indapamide on serum (Na^+) and (K^+) levels in adult male renal hypertensive rats

Treatment	Serum Na^+ level (mmol/dl)	Serum K^+ level (mmol/dl)
Control (hypertensive rats)	170.667±0.265	5.737±0.208
Perindopril (0.08 mg/kg)	199.896±2.154*	5.992±0.284
Amlodipine (0.15mg/kg)	163.186±3.525	5.873±0.253
Metoprolol (0.005mg/kg)	174.246±6.259	5.535±0.153
Indapamide (0.5mg/kg)	158.449±4.928*	4.933±0.108*

Data are presented as mean ±SE

* Significantly different from control value at P<0.05

DISCUSSION

The results of the present study demonstrated that daily administration of perindopril (0.08 mg/kg), amlodipine (0.15 mg/kg), metoprolol (0.005 mg/kg) and indapamide (0.5 mg/kg) for six weeks significantly reduced the development of hypertension-induced hypertrophy in two kidneys on clip renal hypertensive rats. These results are in accordance with our histopathological findings.

Also, results are consistent with studies in animals and patients demonstrating regression in LVH with calcium channel blockers[13,14], ACE inhibitors [15,16], some β-adrenergic blockers[17] and diuretics[18-19]. It might be assumed that the ability of these drugs to cause regression of hypertension induced hypertrophy simply reflects their ability to reduce the systemic vascular resistance responsible for the fall in blood pressure[20].

The greatest effect observed after perindopril in reducing LVH than other antihypertensive classes was in accordance with conclusions based on the recent meta-analysis[21]. Additional mechanisms for perindopril include a specific effect in modification of growth stimulating properties of angiotensin II[22, 23] and a reduction of angiotensin mediated adrenergic outflow.

The ability of calcium antagonists to decrease the hypertension induced hypertrophy may be linked to the fact that hypertrophied cardiac myocytes exhibit a marked increase in inward Ca^{2+} current carried by L-type channels[20] possibly this increase in Ca^{2+} current provides sufficeint Ca^{2+} to trigger the release of additional Ca^{2+} from the internal stores, including the sarcoplasmic reticulum in which cytosolic Ca^{2+} may reach the levels required for stimulation of cell growth.

The poor protection against hypertension induced LVH by β blockers compared with diuretics occurs due to the tendency of β-blockers to increase the ventricular volume whereas diuretics tend to decrease it[18].

In this study, non of the used antihypertensive drugs could induce any significant change in left ventricular nuclear density. Despite the lack in literature, this finding could be supported by the previous study [24] that perindopril reduced the hypertrophy of smooth muscle cells observed in hypertension without altering the deoxyribonucleic acid or protein.

Administration of perindopril for six weeks in two kidneys, one clip renal hypertensive rats insignificantly decreased serum cholesterol and triglyceride levels, but significantly elevated serum HDL. These results are in accordance with many previous reports[25,26]. However, in TOMHS study ACE inhibitor enalapril did not change the lipid pattern over 12 months treatment [19], while Weidmann et al. (1988)[27] reported that ACE inhibitors could not modify, the cholesterol fraction and slightly decreased triglyceride levels.

The present results confirm the neutral effect of amlodipine[28] and indapamide [28,29] on serum concentration of lipids. However, some studies reported an increase in Plasma HDL [30] or plasma triglyceride and cholesterol[30,31] after thiazide diuretics. It has to be noted that the methyl substituted isoindoline part of indapamide differentiates between this agent and other diuretics with harmful effect on lipid profile [28].

Metoprolol a selective β-blocker induced a significant increase in both serum cholesterol and triglyceride levels with a significant reduction in serum HDL. In harmony with the present data, some studies reproted that β-blockers tend to increase total VLDL and triglycerides and decrease HDL and cholesterol [31]. It has to be noted that β-blockade is accompanied by increased adrenergic tone., The latter is known to lower lipoprotein lipase activity[32] which results in increased TG levels due to impaired catabolism of TG rich lipoproteins. Thus, HDL which depends on VLDL catabolsim decreases[27].

Significant change in serum glucose level has only occured after treatment with indapamide. The decrease in serum glucose level may be due to reduction in serum potassium level (observed in this study), or a protective action on carbohydrate metabolism resulting from the differences in the molecular structure compared with other diuretics[28]. The changes in serum blood glucose encountered with indapamid therapy is in agreement with other studies in diabetic and non diabetic hypertensive patients [33, 34].

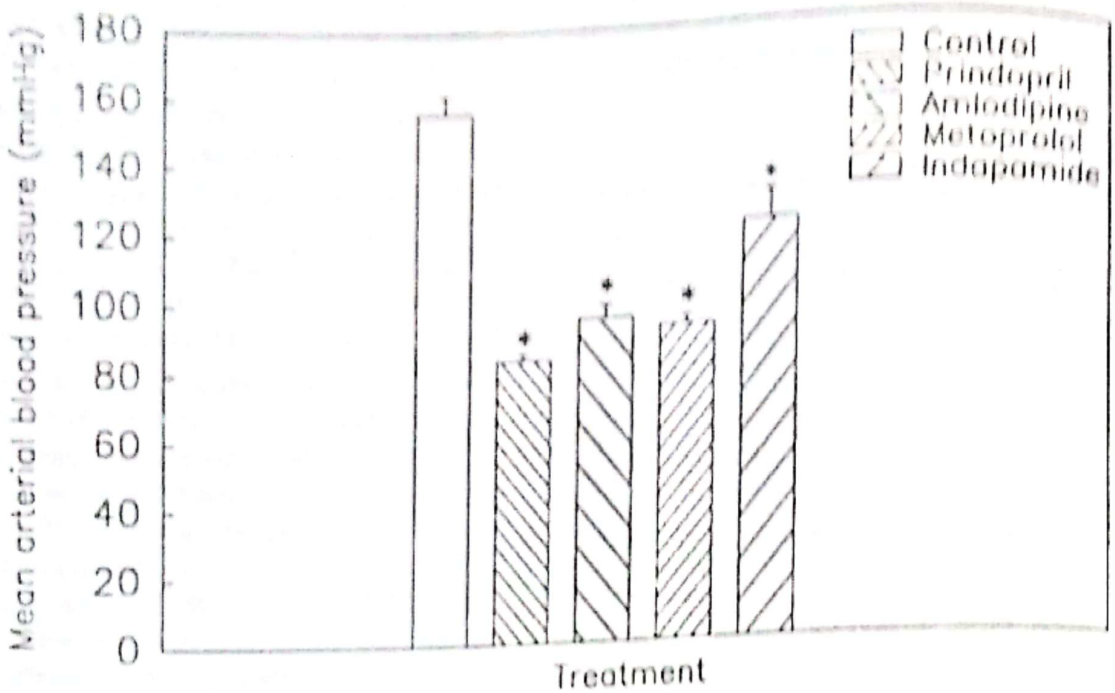

Fig. (1): Effect of perindopril (0.08 mg/kg), amlodipine (0.15 mg/kg), metoprolol (0.005 mg/kg) and indapamide (0.5 mg/kg) on mean arterial blood pressure of adult male renal hypertensive rats.

*** Significantly different from control value at P < 0.05.**

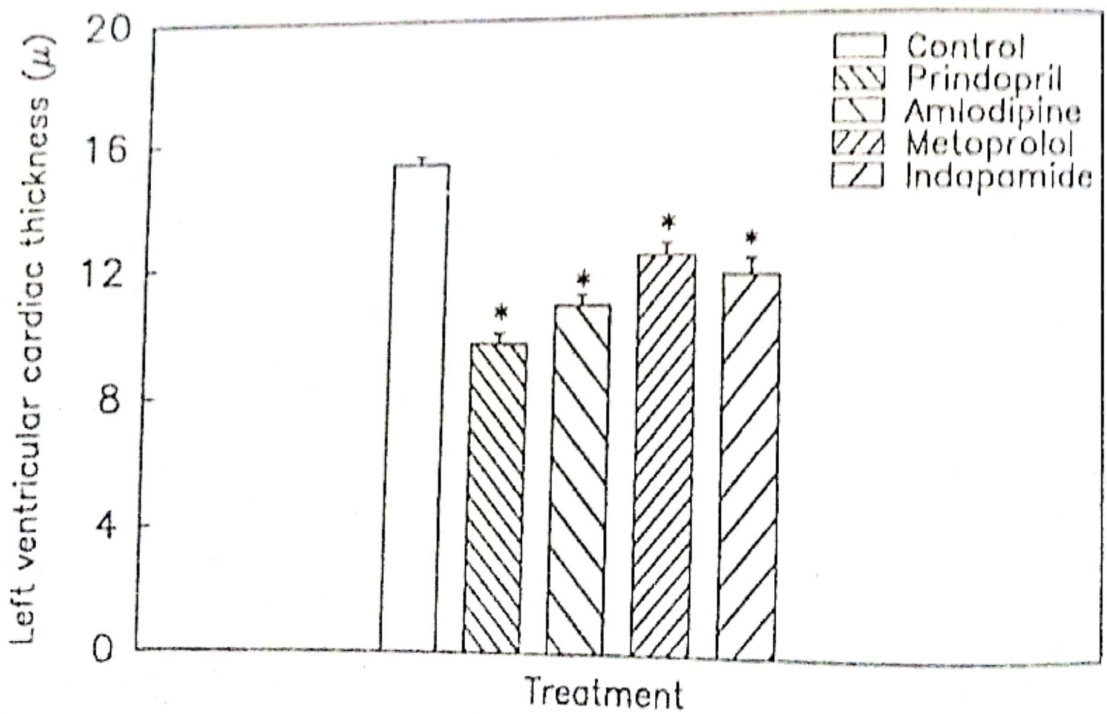

Fig. (2): Effect of perindopril (0.08 mg/kg), amlodipine (0.15 mg/kg), metoprolol (0.005 mg/kg) and indapamide (0.5 mg/kg) on left ventricular cardiac thickness of adult male renal hypertensive rats.

*** Significantly different from control value at P < 0.05.**

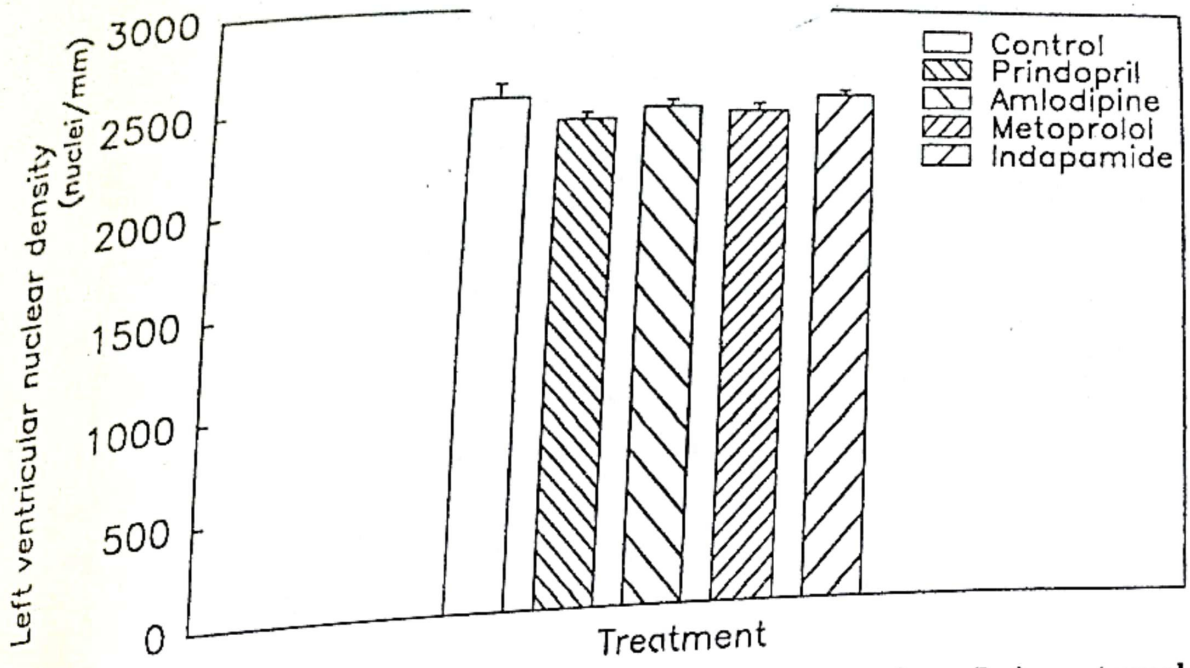

Fig. (3): Effect of perindopril (0.08 mg/kg), amlodipine (0.15 mg/kg), metoprolol (0.005 mg/kg) and indapamide (0.5 mg/kg) on left ventricular nuclear density of adult male renal hypertensive rats.

*** Significantly different from control value at P< 0.05.**

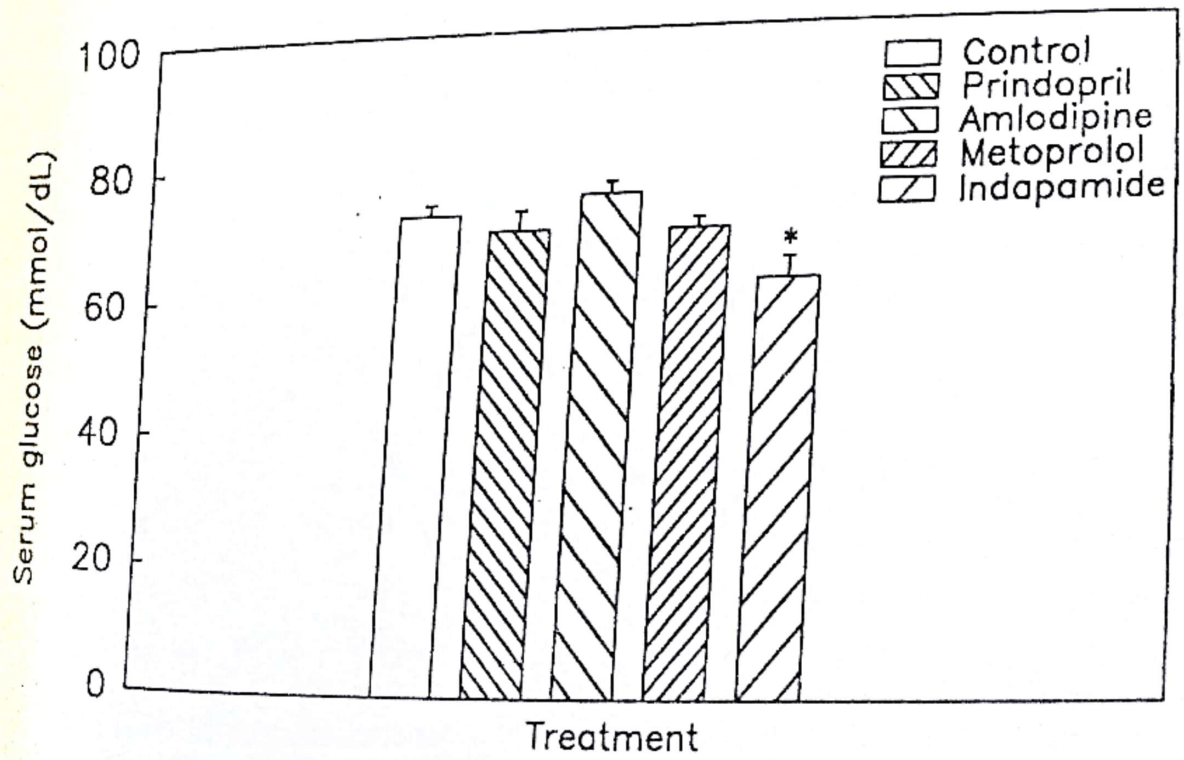

Fig. (4): Effect of perindopril (0.08 mg/kg), amlodipine (0.15 mg/kg), metoprolol (0.005 mg/kg) and indapamide (0.5 mg/kg) on serum glucose level of adult male renal hypertensive rats.

*** Significantly different from control value at P< 0.05.**

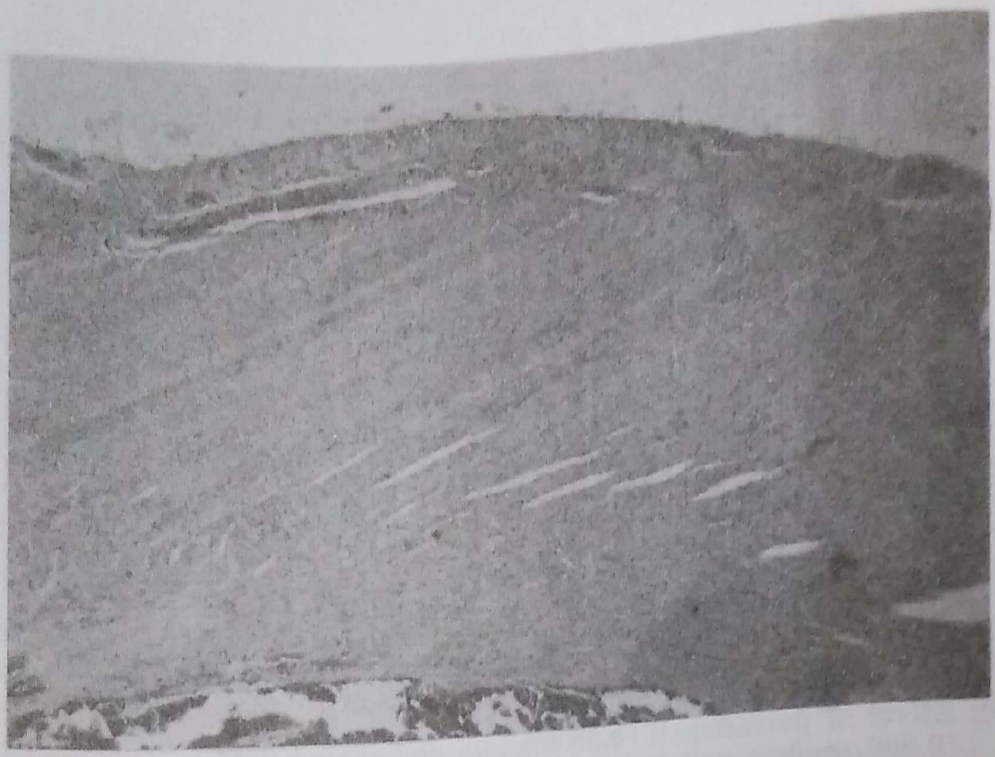

Fig. (5): Left ventricular wall thikness of renovascular hypertensive control group (H x & E x 40).

Fig. (6): Effect of six weeks treatment with perindopril (0.08 mg/kg) on left ventricular wall thickness of renovascular hypertensive rats (H x & E x 40).

Fig. (7): Effect of six weeks treatment with metoprolol (0.005 mg/kg) on left ventricular wall thickness of renovascular hypertensive rats (H x & E x 40).

Perindopril caused a significant increase in serum sodium and insignificant elevation of serum potassium levels which coincised with other reported results[35,36] The increase in serum sodium level is thought to be due to stimulation of renal sodium pump by angiotensin II to enhance the reabsoprtion of sodium by the kidney and hence promote sodium retention[26]

In accordance to the present study, the administration of amlodipine[37] and metoprolol[38] did not induce any significant change in serum sodium and potassium levels. However, a significant decrease in both serum sodium and potassium level was observed following indapamide administration. These results are in agreement with Weidler et al (1995)[39]. Indapamide, a distal tubular diuretic inhibits chloride and sodium reabsorption in the cortical distal dilating segment increasing the delivery of sodium and the rate of flow to the distal nephron and hence stimulates potassium secretion and augments its excretion [40].

The increase in potassium secretion by indapamide is also partly due to the enhancement of intratubular negativily in the distal nephron in consequence to elevated levels of poorly reabsorbed anions that exceed the amount of non reabsorbed sodium present [41].

It could be concluded that, perindopril (an ACE inhibitor) in the present model (2 kidneys one clip renovascular hypertensive rats) seems to have some advantages over amlodipine, metoprolol and indapamide representing other different antihypertensive classes in terms of lowering the elevated blood pressure and protecting against hypertension-induced LVH. It also improved the lipid profile as it increased HDL and seemed to have neutral effect on blood glucose level.

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التأثيرات الوقائيـــة للبرنيدوبريـل والأملوديبين والميتوبرولول والإنداباميد على تضخم البطين الأيسر المستحدث بارتفاع ضغط الدم فى الجرزان ذات ضغط الدم الكلوى المرتفع: دراسة كيميائية حيوية وهستوباثولوجية

نبيلة نور الدين المراغى

قسم الفارماكولوجى - كلية الصيدلة - جامعة الزقازيق - مصر

تهدف هذه الدراسة الى تقييم تأثير تناول أدوية من المجموعات المختلفة المضادة لارتفاع ضغط الدم عن طريق الفم يوميا لمدة ٦ أسابيع فى ذكور الفئران ذات ضغط الدم المرتفع عن طريق سد الشريان الكلوى.

وقد تم دراسة تأثير كل من مثبط تحويل انزيم الانجيوتنسين (برينديريل ٠,٠٨ مجم/كجم) ومغلق قنوات الكالسيوم (املوديبين ١,٥ مجم/كجم) وغالق مستقبلات البيتا (ميتوبرولول ٥٠,٠٠ مجم/كجم) ومدر البول (إنداباميد ٠,٥ مجم/كجم) على ضغط الدم المرتفع وتضخم جدار البطين الأيسر نتيجة لارتفاع ضغط الدم ويقاس هذا التضخم بسمك جدار وكثافة نويات البطين الأيسر.

وقد تم أيضا دراسة تأثير الأدوية المذكورة على التغيرات الأيضية مثل الخاصة بالدهون ممثلة فى الكولستيرول والجليسريدات الثلاثية ودهون البروتين ذات الكثافة المرتفعة وعلى مستوى تركيز سكر الدم وإيونات الصوديوم والبوتاسيوم فى مصل الدم.

وقد أحدث كل من البرنيدوبريل والأملوديبين والميتوبرولول والإنداباميد انخفاضا ملحوظا فى مستوى ضغط الدم المرتفع كما أحدثوا حماية ملحوظة ضد تضخم جدار البطين الأيسر نتيجة لارتفاع ضغط الدم فى حين لم يستطيع أي من هذه الأدوية أحداث تغييرا معنويا فى كثافة النويات.

أحدث الإنداباميد انخفاضا ملحوظا فى مستوى الجلوكوز ومستوى ايونات الصوديوم والبوتاسيوم فى مصل الدم، فى حين أحدث البرنيدوبريل ارتفاعا ملحوظا فى مستوى أيونات الصوديوم.

لم يؤثر أى من الأملوديبين أو الإنداباميد على مستوى الدهون. ولكن البريندوبريل كان له تأثيرا مفيدا بإحداث انخفاضا معنويا فى مستوى دهون البروتين ذات الكثافة المرتفعة.

وعلى العكس أحدث الميتوبرولول انخفاضا فى مستوى دهون البروتينات مرتفعة الكثافة مصحوبا بارتفاع معنوى لكل من الكولستيرول والجليسريدات الثلاثية.

ويستخلص مما سبق فى هذا النموذج من الدراسة (الفئران ذات ضغط الدم المرتفع بسد الشريان الكلوى) أن البريندوبريل له بعض المميزات عن الأدوية الأخرى المضادة لارتفاع ضغط الدم المرتفعة والحماية ضد تضخم جدار البطين الأيسر نتيجة لارتفاع ضغط الدم. كما أن له تأثيرا مفيدا على مستوى الدهون حيث يسبب زيادة ملحوظة فى مستوى دهون البروتينات مرتفعة الكثافة بالإضافة الى عدم إحداثه تغييرا ذا بال فى مستوى الجلوكوز فى مصل الدم.