

A comparison of Indapamide SR 1.5 mg with Hydrochlorothiazide 25 mg, in combination with an ACE-inhibitor, in patients with hypertension and diabetes

The AISHA study

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Abbreviations

ACE-	= Angiotensin Converting inhibitor
EF	= Ejection fraction
FMD	= Flow mediated dilation
HOT	= Hypertension Optimal Treatment
PROBE	= Prospective, parallel, randomized, open, blinded endpoint evaluation
NYHA	= New York Heart Association
SR	= Sustained release

ABSTRACT

Objective: To compare the antihypertensive efficacy and the metabolic effects, as well as the influence on cardiac and arterial function of indapamide SR 1.5 mg with hydrochlorothiazide 25 mg, both in combination with quinapril.

Materials and methods: A minimum number of 50 hypertensive and diabetic patients will be enrolled into the study, for a period of 6 months. They will be randomized either to indapamide slow release 1.5 mg/day, or to hydrochlorothiazide 25 mg/day. Quinapril will be added from the beginning of the study, for a better control of their blood pressure. The dosage of quinapril will be titrated from 10, up to 40 mg/day, as needed for each patient. Apart from clinical and laboratory routine tests, the patients will undergo more specific examinations, such as: ambulatory blood pressure monitoring, for quantifying the antihypertensive effect of the two investigational drugs; conventional and tissue Doppler echocardiography, for cardiac function evaluation; vascular ultrasound examination, for assessing endothelial function and arterial stiffness. This study will provide more comparative data between indapamide and hydrochlorothiazide, in combination with quinapril, concerning not only on their antihypertensive effect and safety, but also their influence on cardiac and vascular function.

Keywords: indapamide, hydrochlorothiazide, cardiac and vascular function, hypertension, diabetes.

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BACKGROUND

Diabetes mellitus holds one of the highest cardiovascular risk, increasing morbidity and mortality rate (1,2). It has recently become an equivalent of coronary heart disease. Most part of its complication develops in large arteries, macroangiopathy, but also in small vessels, microangiopathy (3). Maintaining a good glycemic control does not guarantee the lack of cardiovascular events in diabetic patients. It is highly important to assess and to treat other risk factors and diseases coexisting with diabetes mellitus. When added, hypertension increases even more the number of cardiovascular events (4).

Hypertension treatment in patients with type 2 diabetes mellitus is still a difficult clinical problem. New European guidelines on hypertension and diabetes (5,6) recommend a target blood pressure of less than 130/80 mmHg. Indeed, it was shown by the Hypertension Optimal Treatment study (HOT study) that reducing diastolic blood pressure to 81 mmHg instead of 84 mmHg, the number of major cardiovascular events is reduced by 51% (7). However, only 25% of the patients with hypertension and diabetes reach the target of 130/80 mmHg in routine clinical practice (5-8). Therefore, combination therapy is always recommended (5,6). This should include a diuretic; however, none of the two guidelines makes any recommendations regarding which is the best diuretic therapy in hypertensive patients with diabetes.

Apart from aiming blood pressure using a certain combination therapy, we should always assess its effect on cardiac and vascular function. Both diabetes and hypertension are responsible for a wide range of cardiovascular complications. Most of them arises from endothelial dysfunction, oxidation, inflammation, and vascular remodeling, and contribute to atherogenesis (9).

Clinically evident cardiac changes may take years to develop, but techniques, such as echocardiography, are able to detect structural and functional changes long before symptoms appear. Thus, tissue Doppler echocardiography provides a particularly useful tool for revealing subtle systolic and diastolic dysfunction. This technique quantifies longitudinal and circumferential cardiac contraction, due to the

longitudinal and respectively, radial myocardial fibers contraction. Assessing these parameters might be important, since there are studies showing that patients who have type II diabetes, but no clinically apparent heart disease, nonetheless have impaired longitudinal function of the left ventricle both in systole and diastole, with reduced systolic functional reserve (10).

Meanwhile, several studies showed that hypertension and diabetes lead to a rise in arterial stiffness (11,12), due to endothelial dysfunction. This is one of the mechanisms of impaired longitudinal function, being showed that increased conduit arterial stiffness causes subendocardial longitudinal dysfunction (13).

High-resolution vascular echo is nowadays recommended and validated for the assessment of endothelial function (5). This technique assesses vascular reactivity at the brachial artery level by flow mediated dilation (FMD). The vascular function assessment also includes ultrasound of large arteries in order to evaluate vascular structural changes (by measuring intima-media thickness), and different arterial stiffness parameters, using the *echo-tracking* technique (14).

Indapamide is a diuretic with special characteristics, which was shown to provide cardio- and renal protection in hypertensive patients. Meanwhile, it has similar antihypertensive effects with amlodipine and hydrochlorothiazide (15). Intrinsic mechanisms are probably related to the antioxidant properties (16), and also to the action on the calcium channels (17). Moreover, when compared with hydrochlorothiazide, indapamide has no adverse lipid effects (18), and seems to increase renal function (19). However, a recent study in patients with hypertension and diabetes suggested no superiority of indapamide over hydrochlorothiazide on different metabolic parameters (20). Therefore, new research looking in more detail to the comparison between the two diuretics is mandatory. □

DESIGN

The aim of this study is to evaluate the effects of indapamide SR 1.5 mg on blood pressure, blood tests (glucose metabolism, lipids, minerals, and uric acid), cardiac function, endothelial and arterial function, by comparison with

hydrochlorothiazide 25 mg, in patients with hypertension and type II diabetes mellitus. In order to achieve a better control of blood pressure in these patients, both diuretic treatments will be added to an ACE inhibitor (quinapril 10-40 mg/day). Therefore, eventually, the study will provide data on the comparison between combination indapamide SR 1.5 mg + quinapril versus hydrochlorothiazide 25 mg + quinapril.

A minimum number of 50 male and female patients will be enrolled into the study. Inclusion criteria are: patients more than 18 years old, in sinus rhythm, with daytime ambulatory blood pressure >140 and/or >90 mmHg, **and** type II diabetes mellitus. The main exclusion criteria are: patients with symptoms of congestive heart failure (NYHA III or IV) or left ventricular global systolic dysfunction (EF <40%); ventricular aneurysm or extensive wall motion abnormalities; recent (<6 months) myocardial infarction; recent (<3 months) or planned coronary revascularization; severe valvar/congenital heart disease; creatinine level >1.5 mg/dl for men and >1.4 mg/dl for women; pregnancy or patients who plan to become pregnant during the study period (only for female subjects); history of hypersensitivity to indapamide, quinapril, thiazides or to any of the components of the products; or other important medical condition known to interfere with the study protocol.

Patients will be randomized to either indapamide prolonged-release 1.5 mg/day or hydrochlorothiazide 25 mg/day, given orally. Quinapril will be added from the beginning of the study to allow consistent blood pressure control. Dose of quinapril will be titrated from 10 mg/day up to 40 mg/day, as needed for the blood pressure control. The treatment will be administered for 6 months. Any antihypertensive medication will be stopped at least two weeks prior to randomization.

All patients will be evaluated clinically and by laboratory tests (blood and urine samples). Ambulatory blood pressure monitoring (24 hours) will be used in order to decide the

inclusion of patients, and the antihypertensive efficacy of the study medication. Conventional and tissue Doppler echocardiography will be performed in order to assess cardiac function. Ultrasound assessment of large artery function and endothelial function will be used in order to evaluate morphological changes in the common carotid artery (vascular structural changes and arterial stiffness parameters), and vascular reactivity at the brachial artery level by flow mediated dilation. All analysis will be done off-line by an investigator blinded to the randomization and patient medication (PROBE design). □

DISCUSSIONS

The coexistence of diabetes and hypertension almost doubles the risk of cardiovascular events (7,21-23). It seems to be very clear that we apparently need to focus on controlling both diseases in order to lower global cardiovascular risk.

It has been shown that controlling the blood pressure levels in diabetic patients leads to a dramatically decrease in cardiovascular events and mortality, within a 4- to 6-year period (7,22,24-27); the risk reduction is greater than in non-diabetic population with similar blood pressure levels (7). Furthermore, hypertension control appears to be more effective than glycemic control in reducing microvascular events (26,28).

Aggressive blood pressure control can be achieved only by combination therapy, including a diuretic. The most recent guidelines (5,6) still do not make a clear indication which diuretic would be more effective, with least adverse events. We hope that this study provides valuable data on the comparison between indapamide SR 1.5 mg versus hydrochlorothiazide 25 mg regarding the antihypertensive effects and the metabolic changes, both in combination with quinapril. Meanwhile this study will assess the impact of the two diuretic treatments on cardiac and arterial function, and on the ventriculo-arterial interaction. □

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