Impact of a Low-Dose Reserpine/Thiazide Combination on Left Ventricular Hypertrophy Assessed with Magnetic Resonance Tomography and Echocardiography

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Summary

This was the first study to investigate the capability of a low-dose combination of reserpine and the thiazide clopamide to induce regression of left ventricular hypertrophy (LVH). 20 Caucasian patients (12 men and 8 women, mean age 59 ± 13 years) with arterial hypertension and LVH were treated in an open, intra-individual comparison with a fixed combination of reserpine 0.1mg and clopamide 5mg once daily. At baseline, after 12 and 24 weeks of treatment, wall thickness of the patients' left ventricles and left ventricular function were assessed by ECG-triggered magnetic resonance tomography (MRT) and by echocardiography. The medication was well tolerated. In all patients, diastolic blood pressure was normalised. During the course of therapy, mean systolic/diastolic blood pressure showed a marked decline by −21.7/−17.2mm Hg (2p < 0.0001). Heart rate was significantly lowered by 3.7 beats per minute. Mean end-diastolic interventricular septum thickness measured by MRT was reduced from 11.8mm by 15% (2p < 0.00001) after week 24, systolic posterior wall thickness by 10% (2p = 0.002) and diastolic posterior wall thickness by 20% (2p = 0.0001). Left ventricular end-diastolic and end-systolic inner ventricular diameters quantified by MRT showed no significant changes after 12 and 24 weeks of treatment. Ejection fraction increased from 64% by 8% after 24 weeks (2p < 0.0005). These findings were confirmed by echocardiography. However, there was no significant correlation between the parameters derived from the two methods.

In conclusion, a low-dose reserpine/thiazide combination induced a significant regression in LVH and an improvement in haemodynamic parameters after 24 weeks of treatment.
The main cardiac response to primary hypertension is concentric left ventricular hypertrophy (LVH). Data from the Framingham cohort as well as later studies have indicated that LVH is an important independent risk factor for congestive heart failure, coronary artery disease, stroke, arrhythmia and sudden death. \[1\]

Consequently, pharmacological antihypertensive therapy not only aims at normalising elevated blood pressure, but also at inducing regression of cardiac hypertrophy. Studies in animals and clinical trials indicate that antihypertensive agents from different classes induce regression of LVH to a different extent that is not strictly correlated to the degree of blood pressure reduction. \[6\]-\[11\]

For the four main groups of antihypertensive agents, there is a plethora of studies concerning their capability to reduce regression of LVH. A recent meta-analysis suggested that ACE inhibitors seem to be more potent than β-blockers and diuretics in the reduction of left ventricular mass index; calcium antagonists were somewhat in the intermediate range. \[12\] However, to date there is no study on the effect of reserpine in first-line treatment, despite the fact that reserpine-thiazide combinations have been in clinical use for nearly 40 years \[13\] and are still among the most frequently prescribed antihypertensives in countries such as Germany, Switzerland and South Africa.

Therefore, the effect of reserpine in combination with the thiazide clopamide, given in low doses once a day, was evaluated in this clinical study. With the use of magnetic resonance tomography (MRT) \[14\]-\[16\] and echocardiography we employed sophisticated and highly reproducible and reliable methods.

Patients and Methods

Patients

Outpatients aged over 18 years with a sitting systolic blood pressure (SBP) over 140mm Hg and a sitting diastolic blood pressure (DBP) between 100 and 114mm Hg after a 2-week placebo period in addition to LVH were considered for inclusion in the study. LVH was defined as an end-systolic septal thickness ≥ 15mm and systolic posterior wall thickness ≥ 14mm Hg in echocardiography.

The main exclusion criteria were pretreatment with any other antihypertensive drugs affecting blood pressure within 6 months preceding entry into the study, secondary hypertension, cerebrovascular insult less than 6 weeks previously or known cerebral blood flow disturbances (such as transient ischaemic attacks), unstable angina or myocardial infarction in the previous 3 months, heart failure not controlled by digitalis, impaired renal or hepatic function, colitis and/or gastroenteritis or ulcers, other serious concomitant diseases, drug or alcohol abuse, and mental impairment.

Study Design and Methods

This single-blind, open study was approved by the local ethics committee and patients gave their written informed consent to participate. The design included a 2-week placebo run-in period, which was followed by verum treatment for 24 weeks. Patients were administered a fixed low-dose combination of reserpine 0.1mg and the thiazide diuretic clopamide 5mg (Briserin®, Novartis Pharma GmbH, Germany), which had to be taken once daily in the morning. If diastolic blood pressure was not normalised after 6 weeks of therapy (i.e. DBP ≤ 90mm Hg), the dose was doubled from week 7 to 24.

A complete physical examination including a 12-lead electrocardiogram was performed at baseline and at the end of the study. Blood pressure was measured with a standard mercury sphygmomanometer according to the American Heart Association guidelines \[17\] after a 5-minute rest; the mean value of 3 measurements was used in the calculations. Patient compliance was checked by means of pill counting at every visit. Standard fasting laboratory tests were performed during the placebo phase and at the end of the study. Adverse events were assessed at each visit by recording spontaneous reports. Target measurements were performed with MRT and echocardiography at baseline, after 12 weeks and at 24 weeks.