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PhD THESIS

ABSTRACT

PHARMACOLOGICAL, CLINICAL AND
EXPERIMENTAL STUDY ON THE ASSESSMENT OF
THERAPY WITH AMLODIPINE, VALSARTAN AND
HYDROCHLOROTIAZIDE TO OPTIMIZE APPROACH TO
GERIATRIC PATIENTS WITH
ARTERIAL HYPERTENSION

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fixed-dose combination Amlodipine + Valsartan + Hydrochlorothiazide 10/320/25 mg, adherence, compliance and persistence of treatment, zinc bioavailability, copper serum levels, copper/zinc ratio, reduction of the lithogenic risk, hypertensive geriatric patients.

ABSTRACT

This doctoral thesis entitled: **"Pharmacological, clinical and experimental study on the assessment of therapy with amlodipine, valsartan and hydrochlorothiazide to optimize approach to geriatric patients with arterial hypertension"**, provides a current approach overview on the arterial hypertension of the elderly, which represents a complex issue of pharmacogeriatrics.

The study was conducted in a total of 235 multiple-comorbid hypertensive geriatric patients who were treated with the triple combination at fixed doses of 10/320/25 mg with amlodipine, valsartan and hydrochlorothiazide over a three-year study period, whose blood pressure has not previously been adequately controlled with other treatment regimens administered as monotherapy or dual therapy. Important aspects of the practitioner's work were deepened, namely the efficacy and therapeutic safety of this treatment regimen, the adherence and the factors that influence it, as well as other beneficial effects of triple therapy in the geriatric patient (improvement of electrolyte, urinary excretion of zinc, of the Cu/Zn ratio, the reduction of the serum calcium and the reduction of the lithogenic risk in patients with associated renal lithiasis comorbidity).

The thesis is divided into two distinct parts; **in the general data for the study of literature in the field of research**, one presents a synthetic material selected and extracted from the published literature which reflects the latest information on pharmacological data on the hypertensive geriatric patient approach.

The general part, organized in two major chapters, describes in the first chapter the present stage of knowledge about the pharmacological changes that occur in the geriatric hypertensive patient's body. The subchapter on the "pharmacokinetics of the geriatric patient's body" makes an insight into current data on the absorption, distribution and elimination of drugs. Described are issues related to the administration of geriatric antihypertensive therapy, the personalization of therapeutic regimens, the adherence to treatment and the factors that influence it. *Polypharmacy* is a major problem in the hypertensive geriatric patient. One addressed and discussed *the comorbidities* which impose the need to administer loaded treatment regimens. The concepts of the principles of choosing antihypertensive drugs, the initiation, the monitoring of therapy and the rules governing the transition from monotherapy to dual therapy and triple therapy are addressed.

There are listed and explained the causes leading to non-adherence and reduction of therapeutic compliance, the approach of measures to reduce the cardiovascular risk of geriatric patients.

The individualization of treatment regimens is required with the individuality of each case, depending on the severity of the underlying disease, the number and severity of the comorbidities of each patient and the degree of multisystem organ failure caused by the senescence process. An important aspect for therapeutic practice is the deepening of *drug interactions* that have repercussions on *non-adherence to treatment*.

The last part of the data concerning the theoretical incursion of the researched field refers to a very topical issue for the practitioner, namely triple therapy with amlodipine, valsartan and hydrochlorothiazide in fixed doses administered as a single pill. Theoretical data are presented on the pharmacokinetic and pharmacodynamic behavior of each of the representatives of the combination individually, with *linear kinetics* being noted - which explains the very good tolerability and lack of drug interactions. Also, *the pharmacological behavior of the global association of triple antihypertensive therapy* as well as *the safety and therapeutic effectiveness data* are explained extensively by discussing the research conducted in this field.

Own experimental research describes the research methodology applied in three experimental studies performed on a number of 235 hypertensive geriatric patients, and respectively, associated comorbidities. *Research methods*, qualitative and quantitative, refer to a retrospective analysis over a 3-year period of the database obtained from a study performed during the years 2014 and 2017. The research was conducted in accordance with the principles of the Helsinki Declaration (*"Ethics and Epidemiology: International Guidelines"*) published by the Council for International Organizations of Medical Sciences. Each of the three studies adhered rigorously to the inclusion and exclusion criteria.

Each patient was analyzed according to a general study protocol, and the study methodology was very complex, experimental, giving the thesis a valuable interdisciplinary character, the results achieving a symbiosis with pharmacology, internal medicine, biochemistry and mineralogy.

In the global study group, the tightened tension values were compared after triple therapy, and the adhesion was evaluated based on the Morisky-Green-Levine Therapy Adhesion Scale (MMAS-4).

The 235 eligible patients with hypertension were divided into three groups in three studies, respectively:

- 90 geriatric hypertensive patients in study I;
- 82 geriatric hypertensive patients in study II;
- 63 geriatric hypertensive patients with renal lithiasis in study III.

Study I - entitled *"Interference between antihypertensive treatment regimens and the bioavailability of zinc in geriatric patients"* had the following **research protocol**: in an 8-month, open, experimental, comparative and retrospective study, carried out between 01.01.2014-30.09.2014, at the Timis County Center within the Ministry of Internal Affairs, Timisoara, Romania, 90 geriatric patients were enrolled which 42 female (46.67%) and 48 males (53.33%). The mean age was 74.2 ± 3.4 years (the reference range being 65-80 years). Subjects were divided into two study groups according to their antihypertensive therapy:

- Group I - 45 subjects treated with captopril alone in the form of 50 mg tablets administered in two daily intakes;
- Group II - 45 subjects treated with Aml + Val + HCTZ 10/320/25 mg single dose triple therapy as one tablet per day.

All patients received a 44 mg zinc sulphate supplement administered twice daily for 8 months. Variations in serum zinc concentrations were evaluated before treatment and again 4 months later and at the end of the study period. Zinc samples in urine were analyzed comparatively before the start of treatment and at the end of the 8 months of daily supplementation.

Study II - entitled *"Beneficial Effects of Triple Antihypertensive Therapy with Amlodipine, Valsartan and Hydrochlorothiazide on Copper Status in a Trial of Geriatric Patients in Southwestern Romania"* had the following **research protocol**: the study was conducted over a period of 3 years, between April 2014 and May 2017, in a total of 82 hypertensive geriatric patients aged 65-80 years with a mean age of 68.4 ± 2.6 years. Patients were diagnosed with hypertension based on the criteria of the European Society of Cardiology. The purpose of this study was to evaluate the beneficial pharmaco-therapeutic effects of Aml + Val + HCTZ triple therapy on copper status in a group of hypertensive geriatric patients. In this respect, copper values were determined by atomic absorption spectrophotometry. Cu/Zn ratio values were determined dynamically by atomic spectrometry at the Toxicology Laboratory of Timișoara County Emergency Hospital. The determinations were performed comparatively - initially and at the end of the study period.

Study III - entitled *"Biochemical, pharmacological, and therapeutic effects of triple antihypertensive therapy with amlodipine, valsartan and hydrochlorothiazide in elderly hypertensive patients with calcium phosphate nephrolithiasis"* had the following **research**

protocol: this experimental study was conducted between June 1 2014 and July 31 2017. Patients aged 65-75 years were given Aml + Val + HCTZ 10/320/25 mg triple single dose therapy. All patients enrolled in the study had *renal urinary lithiasis* - a condition they had suffered for many years prior to triple therapy as antihypertensive therapy. By taking into account the effects of thiazide diuretics (hydrochlorothiazide) on the reduction of the lithogenic risk - we have confirmed this scientific observation on our study group - by monitoring calcium episodes, crystalluria and renal urinary calculus. The *lithogenic risk* assessment was performed by monitoring the urine supersaturation through the Finyalson test, and the lithiasis and microlithiasis were examined by Fourier Transform Infrared Spectroscopy and X-ray diffraction.

The results chapter is the most extensive, it contains the analysis of the results of the three studies, the presentation of which is ensured on the one hand by a succession of tables and graphs relevant to the topic of the PhD thesis, as well as exemplifying some representative cases.

The results of the total study group of 235 patients showed primarily the change and comparative evaluation of systolic tension values of geriatric patients under the triple therapy from an initial average of 168.17 ± 5.64 mmHg to a mean final value of 139.97 ± 4.69 mmHg. Detailed statistical analysis reveals for the patient group at baseline that diastolic blood pressure decreased from an average of 96.76 ± 4.55 mmHg to an average of 79.34 ± 5.07 mmHg. Based on the *number of comorbidities* present at enrollment in the study, the following suggestive situations were differentiated: the presence of 2 comorbidities - 112 patients (47.66%) and 3 comorbidities - 80 patients (34.04%). Polypharmacy was noted in 130 (55.32%) of patients who received between 6 and 8 medications daily. *Adherence to treatment* was quantified after 1-year Aml + Val + HCTZ triple therapy - according to the *Morisky adherence scale*. In 82% of subjects, high adherence was noted, in 14% of cases - intermediate adherence, and in only 4% of geriatric patients - low adherence. *Adverse reactions* reported by geriatric patients at the end of the triple therapy at fixed doses of Aml + Val + HCTZ were noted in only 48 patients in the total 235 group, respectively in a percentage of 20.42%.

The results of Study I revealed that all hypertensive geriatric patients enrolled had insufficient zinc levels below the normal serum zinc standard (<70 $\mu\text{g/dL}$) at the start of the study. The mean and variance in the three assessment moments of serum zinc concentrations showed the following variations: at baseline or respectively the start of the study (Zinc Month 0) - the mean serum zinc was 58.44 $\mu\text{g/dL}$ and the variance was 24.7 ; after 4 months of daily supplement (Zinc Month 4), the mean serum zinc concentration reached 65.24 $\mu\text{g/dL}$, and the variance was 39.69 ; at the end of the study (Zinc Month 8) the mean serum zinc concentration reached 74.22 $\mu\text{g/dL}$, exceeding the inadequacy threshold, and the variance was 34.59 . With regard to the 24-hour urine zinc excretion monitoring, it was noted that a significant increase in urinary zinc excretion after 8 months of treatment was only observed in study group 1 treated with captopril. Results for urinary zinc excretion in the group 2 - treated with triple therapy Aml + Val + HCTZ 10/320/25 mg - are significantly different from the first group treated with Captopril, in which case the beneficial effect of the combination is exerted by the much decreased urinary zinc excretion (mean and standard deviation was initially 282.71 ± 3.39 mcg/24 h and after 8 months of treatment reached 292.09 ± 4.28 mcg/24 h).

The results of Study II have shown in 82 eligible patients that serum copper concentrations at the extreme times of the study (initially and at the end of the 3 years of administration of Aml + Val + HCTZ 10/320/25 mg) were between $8, 20 \pm 12.10$ $\mu\text{mol/L}$ and 12 ± 4.0 $\mu\text{mol/L}$. Values of the Cu / Zn ratio in the extreme times of the study (initially and at the end of 3 years of Aml + Val + HCTZ 10/320/25 mg) increased from 0.80 ± 6.2 $\mu\text{mol/L}$ to 0.9 ± 1.4 $\mu\text{mol/L}$.

The results of Study III showed that in this extended study over 3 years, 63 patients, 28 (44.44%) women and 35 men (55.56%) were enrolled. Of the eligible subjects, 5 patients

(7.94%) had *kidney stones*, and 58 patients (92.06%) had *recurrent episodes of crystalluria with microlithiasis*. All patients had similar blood pressure values and tension values were well controlled throughout the trial under triple therapy. Overall, triple fixed dose Aml + Val + HCTZ 10/320/25 mg treatment reduced the lithogenic risk by modifying the following parameters illustrating urinary supersaturation:

- phosphaturia – from the initial values of 904 ± 32 mg/day at 612 ± 18 mg/day;
- **calciuria** – from the initial values of 256 ± 14 mg/day at 148 ± 28 mg/day;
- oxaluria – from the initial values of 34 ± 18 mg/day at 21 ± 16 mg/day.

At the end of the three years of the study, significant recurrence reduction was found by 50% - and in the case of the calculations constituted - in the five patients, they had only a calcium phosphate composition and a high degree of fragility compared to the previous kidney stones of the patients, previously to the triple therapy (Aml + Val + HCTZ) administration. Examining of the kidney stone samples was performed by two structural methods - FT-IR spectroscopy and X-ray diffraction, respectively. Fourier Transform Infrared (FT-IR) absorption spectra and diffractograms from the kidney stones obtained from the five patients - are individually illustrated, along with the metabolic status of each case, as measured by the detailed calciuria values (which recorded the most important decrease), as well as urinary phosphate and oxaluria. Magnesium and ammonium phosphate hexahydrate are the most commonly encountered phosphatic mineralogical phases in kidney urinary calculi obtained from geriatric patients, being synthesized under high pH conditions (between 6.5-8).

Statistical and mathematical correlations on the study groups were made by presenting the results of the studies in the form of tables, percentages, mean values, standard and median deviations. Data correlation and value distribution determination was used with the Analysis Tools in Excel in Microsoft Office 365. The ANOVA: Single Factor and Descriptive Statistics methods were used to determine the median and variance.

The discussion part of the doctoral dissertation is the most valuable, the complexity of the emphasized aspects having the role of elucidating the pharmacological processes, as well as the therapeutic ones in the field of pharmacogeriatrics.

Discussion on Study I refers to the zinc values excreted in group I of patients treated with captopril, in which the difference between baseline and final was high - 320 mcg / 24 h); in the second group - treated with the triple combination of Aml + Val + HCTZ, the difference between baseline and final value was small – only 100 mcg/24 h. Results from this study support these findings and explain the significant increase in urinary zinc excretion in urine collected over 24 hours due to captopril therapy - by the interference of zinc bioavailability with metal catalyzed reactions. It is the merit of several teams of researchers coordinated by Leary et al. (1992), Fernandes et al. (1996) as well as Golik et al. (1998) - who have found that angiotensin converting enzyme inhibitors, captopril and enalapril, have functional groups such as sulfhydryl or carboxyl, whose zinc binding capacity determines the mineral status of the body. Normalization of zinc balance in hypertensive geriatric patients is particularly beneficial in patients who have comorbidities of autoimmune or polyarthritis, antioxidant and anti-inflammatory effects. Correlation of variations in serum zinc concentrations with the number and type of co-morbidities of each hypertensive geriatric patient, as well as a complete history of balanced diet and lifestyle change, is a very important measure to combat zinc deficiency and restore balance of minerals to the geriatric hypertensive patient.

Discussion on Study II Numerous observational studies have shown that zinc (Zn), copper (Cu), magnesium (Mg) and manganese (Mn) in the serum play an essential role in the pathophysiological processes involved in the geriatric patient's hypertension. These biometals have been shown to work on the intracellular oxidative balance and the renin-angiotensin system. **Copper** is a complex trace element with pleiotropic effects, but changes in its

elementary state in human fluids in geriatric patients are divergent and not yet fully understood. One predictive factor is **the Cu/Zn ratio** associated with severity of cardiovascular damage.

- At baseline, geriatric patients enrolled in the initial study had a significant copper deficiency as an expression of the nutritional deficiency of specific microelements in this age group. The initial serum copper level was $8.2 \pm 12.1 \mu\text{mol/L}$, with no differences between patients between the two sexes ($p = 0.682$). After 3 years of triple therapy in combination with fixed doses of Aml + Val + HCTZ 10/320/25 mg, there was a significant increase in the values at $12.3 \pm 4.0 \mu\text{mol/L}$;
- Copper values have reached the lower end of the reference range for serum copper concentrations; for these reasons - a balanced diet with copper supplementation is required - in hypertensive geriatric patients;
- The initial Cu/Zn ratio was $0.8 \pm 6.2 \mu\text{mol L}$. After 3 years of triple therapy in combination with fixed doses of Aml + Val + HCTZ 10/320/25 mg, there was a significant increase in the values at $0.9 \pm 1.4 \mu\text{mol / L}$, which contributes to the reduction cardiovascular risk in patients enrolled in the study.

Discussion on Study III Over the last decade, research has been carried out in the interdisciplinary field of pharmacogeriatrics, which shows that thiazides can exert a beneficial effect in patients with renal lithiasis and hypertension by decreasing calciuria and preventing lithogenic risk. So far, there is no evidence to investigate the effects of triple therapy with amlodipine, valsartan and hydrochlorothiazide on reducing the lithogenic risk in hypertensive geriatric patients. In this regard, we conducted a study of 63 hypertensive geriatric patients with pre-existing renal urinary lithiasis. Among the patients under study, 42 (70%) were over 10 years of age, with a high risk for recurrence of renal lithiasis episodes. The lithogenic risk was monitored by the frequency of recurrences - clinically manifested by crystalline episodes or urinary constrictions, confirmed by ultrasound or radiographic evidence.

Studies in this thesis allow formulation of the following **original contributions and conclusions for practice**:

Interference between antihypertensive treatment regimens and the bioavailability of zinc in geriatric patients

- Selective antihypertensive drugs may affect mineral status in geriatric patients and specifically influence the bioavailability of zinc;
- Zinc has proven effective in geriatric patients with high blood pressure because it is a mineral that plays the role of an important antioxidant and anti-inflammatory agent, while exerting beneficial effects against atherosclerosis and heart failure, improving the quality of life of these patients;
- The initial results of the study showed the zinc deficiency - as an electrolyte deficiency factor present in all hypertensive geriatric patients, both in group I, treated with Captopril alone and in group II patients, with Aml + Val + HCTZ 10/320/25 mg administered as a single dose;
- The final results for urine zinc excretion in the group of patients treated with Aml + Val + HCTZ triple therapy are significantly different from the first group treated with Captopril alone, in which case the beneficial effect of the combination is exerted by the much more decreased level of zincuria;
- Long-term therapy with Captopril causes an excessive zinc deficiency in hypertensive elderly patients compared to triple antihypertensive combined therapy with fixed dose, which is safer and with fewer side effects;
- Knowing these issues is important for health care providers who have hypertensive geriatric patients under surveillance.

Beneficial Effects of Triple Antihypertensive Therapy with Amlodipine, Valsartan and Hydrochlorothiazide on Copper Status in a Trial of Geriatric Patients in Southwestern Romania

- Copper is one of the biometals that act on the intracellular oxidative balance and the renin-angiotensin system, important for the hypertensive geriatric patient;
- The correlation between low serum copper levels and ferriprive anemia in hypertensive patients is important for the practitioner;
- Triple therapy in combination with fixed doses of Aml + Val + HCTZ 10/320/25 mg causes increased Cu/Zn ratio and cardiovascular risk reduction, with beneficial effects especially for hypertensive geriatric patients who have comorbidities.

Biochemical, pharmacological, and therapeutic effects of triple antihypertensive therapy with amlodipine, valsartan and hydrochlorothiazide in elderly hypertensive patients with calcium phosphate nephrolithiasis

- The mechanism of action of hydrochlorothiazide is based on decreased calcium and urinary pH changes in supersaturated urine;
- In hypertensive geriatric patients - treatment with 25 mg / day hydrochlorothiazide in the fixed dose combination of Aml + Val + HCTZ 10/320/25 mg is effective in reducing the lithogenic risk;
- The lithogenic risk was monitored by the recurrence frequency - clinically manifested by crystalline episodes or urinary calculi, confirmed by ultrasound or radiograph and decreased by 50% in patients who received triple therapy with fixed doses of Aml + Val + HCTZ 10/320/25 mg for 3 years;
- Hydrochlorothiazide prevents lithogenic recurrences in the long term, being indicated for geriatric patients with nephrolithiasis; concretions in hypertensive geriatric patients have a predominantly calcium phosphatic composition and are more friable and soluble;
- Control of electrolythemia is necessary to prevent adverse effects from long-term treatment with hydrochlorothiazide;
- Using Fourier transform infrared spectroscopy (FT-IR) and X-ray diffraction as high-performance analysis methods for the first time, we studied the evolution of the lithogenic process and recurrence risk in hypertensive geriatric patients treated with thiazide diuretics.

Conclusions regarding the total group of hypertensive geriatric patients treated with triple therapy with amlodipine, valsartan and hydrochlorothiazide

- In accordance with the pharmacological and clinical efficacy trials, a significant decrease in the tension values under the triple therapy (Aml + Val + HCTZ) 10/320/25 mg was obtained on the general patient group, and the beneficial changes obtained, noted after six months of treatment and persistence of treatment was high;
- A high adherence to triple therapy with Aml + Val + HCTZ was noted in 82% of subjects;
- Nonadherence cases were due to multiple comorbidities but also to the advanced age of some patients with cognitive impairment;
- The single pill is a very useful therapeutic solution for these patients, by fighting polypharmacy and increasing the quality of their life.

This research belongs to the field of pharmacogeriatrics, by pluriethiological and interdisciplinary approach of the geriatric patient's hypertension, bringing additional original elements for the in-depth knowledge of this condition.