

Biochemical, Pharmacological, and Therapeutic Effects of Triple Antihypertensive Therapy with Amlodipine, Valsartan and Hydrochlorothiazide in Elderly Hypertensive Patients with Calcium Phosphate Nephrolithiasis

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Antihypertensives are widely prescribed in the geriatric population and could influence kidney stone risk but many aspects are still unknown. Thiazides are used to control lithogenic factors and recurrences in patients with calcium lithiasis. The aim of our study was to evaluate the relationship between essential arterial hypertension and stone disease, by studying the pharmaco-therapeutic effects of a fixed-dose combination of amlodipine + valsartan + hydrochlorothiazide (Aml + Val + HCTZ) 10/320/25 mg, on the urinary stone risk in a study group of hypertensive geriatric patients. A longitudinal, randomized, three years follow-up clinical and experimental study was conducted during June 1, 2014 - July 31, 2017. A number of 60 eligible geriatric patients, treated only with a fixed-dose combination of Aml + Val + HCTZ 10/320/25 mg, as a single-tablet, were enrolled in the study. All the patients were stone formers, with more than three episodes of crystalluria in the last two years. The patient's age ranged between 55 and 65 years. Exclusion criteria: patients with heart failure, kidney chronic diseases, use of drugs known to affect renal function, patients with multi-morbidities. All patients had similar blood pressure values, and tension was well controlled throughout the whole study period. In the elderly patients, the treatment with 25 mg/day of hydrochlorothiazide (from the combination of Aml + Val + HCTZ 10/320/25 mg) has a beneficial and prolonged efficacy in treatment of recurrences in patients with calcium oxalate and phosphate lithiasis. Our study reveals that in the elderly patients with hypertension and nephrolithiasis as a comorbidity, thiazides - 25 mg/day of hydrochlorothiazide (from the combination of Aml + Val + HCTZ 10/320/25 mg) has a beneficial effect in order to control lithogenic factors and recurrences in patients with calcium phosphate lithiasis.

Keywords: fixed-dose combination of Aml + Val + HCTZ 10/320/25 mg, hydrochlorothiazide geriatric patient, nephrolithiasis

Research over the past decade has shown that triple fixed-dose combination of amlodipine + valsartan + hydrochlorothiazide (Aml + Val + HCTZ) 10/320/25 mg has beneficial effects and is safe for the elderly hypertensive patients [1- 3].

Geriatric patients have a lot of co-morbidities that make antihypertensive therapy even more difficult. Nephrolithiasis (kidney stone) has a prevalence and incidence that has increased markedly in elderly population [4]. Studies by Knoll T and coworkers have revealed that about 10%-20% of all patients with nephrolithiasis are older than 65 years [5].

Antihypertensives are widely prescribed in the geriatric population and could influence kidney stone risk but many aspects are still unknown [6].

The pathogenic link between hypertension and renourinary stone disease is not fully understood. A possible association between nephrolithiasis and stone risk profile, including supersaturation of lithogenic salts, hypertension has been suggested by a high number of studies [7, 8].

A significant correlation between arterial pressure and calcium excretion has been revealed by many researchers especially in older patients when hypertension is associated with excessive body weight [9-12].

Objectives

The aim of our study was to evaluate the relationship between essential arterial hypertension and stone disease,

by studying the pharmaco-therapeutic effects of a fixed-dose combination of Aml + Val + HCTZ 10/320/25 mg, on the lithogenous risk in a study group of hypertensive geriatric patients.

Experimental part

Material and method

Study design

A longitudinal, randomized, three years follow-up clinical and experimental study was conducted during June 1, 2014 - July 31, 2017. A number of 60 eligible geriatric patients, treated only with a fixed-dose combination of Aml + Val + HCTZ 10/320/25 mg, as a single-tablet, were enrolled in the study. All the patients were stone formers, with more than three episodes of crystalluria in the last two years. The patient's age ranged between 55 and 65 years.

The patients received fixed-dose combination of Aml + Val + HCTZ 10/320/25 mg, as a single-tablet once-daily during the three years study period.

In order to participate in this survey, all 60 patients expressed written consent, according to the criteria set out in the Helsinki Declaration [13].

Inclusion criteria

In the study were enrolled geriatric patients with diagnosis of arterial hypertension according to current European guidelines, with previous calcium phosphate urolithiasis.

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Exclusion criteria

Exclusion criteria: patients with heart failure, kidney chronic diseases, use of drugs known to affect renal function, patients with multi-morbidities [13-17].

Fourier-transform infrared spectroscopic analysis

Infrared absorption spectra were traced with a JASCO FT-IR 4200 device (with automatic reading of the absorption bands, interferometer Michelson 45°). The measuring range was set to 4000-600 cm⁻¹. Spectra were taken at the normal temperature and pressure existing in the laboratory. The smoothness of the line of 100 % T was 100 ± 1.0 % T (repeating the continuous measurement).

The samples were prepared after KBr pelleting, by mixing the ground bone with KBr (1 mg sample/100 mg KBr) under vacuum, as usually applied for *Fourier-transform infrared spectroscopic studies* [18].

The crystalline hydroxyapatite was obtained from amorphous calcium phosphate at pH 8.5; preparation was done by the method of Boskey and Posner [19].

Urinary stone risk evaluation

Supersaturation calculations for calcium oxalate, calcium phosphate, and struvite were obtained using the technique introduced in 1977 by Finyalson B [20].

Statistical analyses were performed using the SPSS software package (version 23.0 for Windows, SPSS Inc, Chicago, IL.). Results were expressed as mean and

standard deviation. The difference was considered significant when the *p*-value < 0.05.

Results and discussions

In the study were enrolled 60 elderly patients, respectively 25 women (41.67%) and 35 men (58.33%). Of the 60 cases evaluated, at the beginning of the study, 8 patients (13.33%) had renal urinary microlithiasis and 52 patients (86.67%) presented macroscopic renal urinary calculi.

All patients had similar blood pressure values, and tension was well controlled throughout the whole study period (*p*>0.05).

The age of the patients enrolled in the study ranged between 55 and 65 years (table 1).

Among the macroscopic kidney stones, 13 cases (21.67%) were eliminated spontaneously, 17 cases (28.33%) were crushed by extracorporeal lithotrithy and 22 (36.67%) required surgical removal.

Each patient underwent a complex examination plan, with anamnestic, clinical and paraclinical steps, as in the example bellow (fig. 1).

The Fourier-transform infrared spectra revealed seven spectral bands, as pointed out in table 2. There are revealed two spectral bands specific to phospho-calcic compounds – the specific band for carbonatapatite - at 793.56 cm⁻¹ and that of hidroxyapatite at 633.50 cm⁻¹, in a female patient with nephrolithiasis since four years and hypertension since only two years, receiving a fixed-dose combination of Aml + Val + HCTZ 10/320/25 mg, as a single-tablet once-daily.

Studied parameter	Nr.	L min.	L Max.	MA	Me	SD	SE
Patients age	60	55	65	61.17	61.00	2.60	0.34

Nr. -No. of subjects; L min. -minimum limit; L Max -maximum limit; MA -arithmetic range; Me -median; SD -standard deviation; SE -standard error.

Table 1
ANALYSIS OF THE PATIENTS AGE ENROLLED IN THE STUDY (60 PATIENTS WITH HYPERTENSION AND NEPHROLITHIASIS)

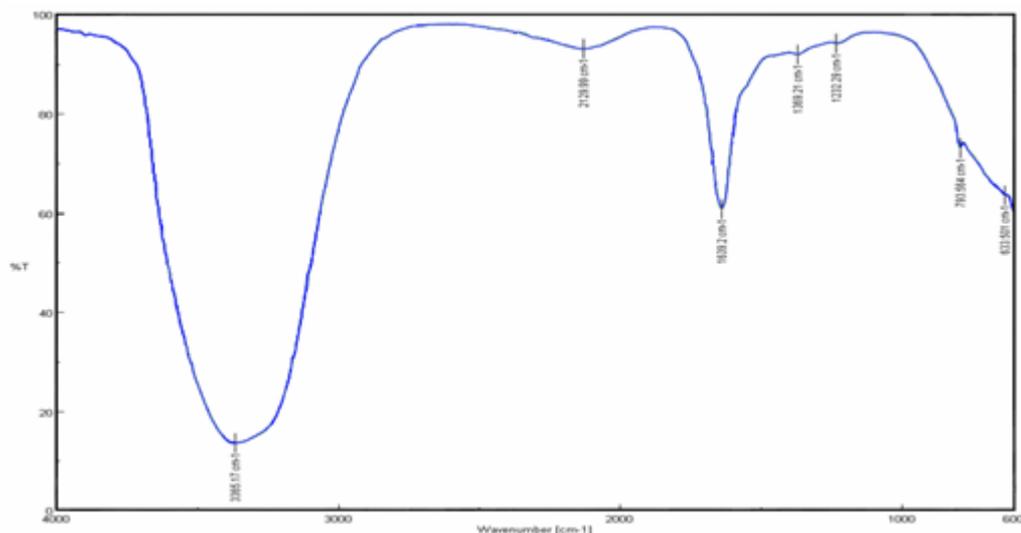


Fig.1. Fourier-transform infrared spectroscopic analysis of a renal calculus from patient M.A., 63 years old with hypertension and nephrolithiasis since four years

Spectral domain (cm ⁻¹)	Compound	Clinical features	Laboratory findings
3365,17	water	Hypertension treated with Aml + Val + HCTZ 10/320/25 mg Phospho-calcic urolithiasis – Renal colic	Recurrent stone former Urinary phosphorus 890 mg/day Calciuria 216 mg/day Oxaluria 33 mg/day
2129,99	CO ₂		
1639,20	lipids and proteines		
1369,21	Amide III		
1232,29	HA		
793,56 633,50	CO ₃ = CA HA		

HA - hidroxiapatite; CA - carbonatapatite.

Table 2
FOURIER-TRANSFORM INFRARED SPECTROSCOPIC ANALYSIS, CLINICAL FEATURES AND URINARY STONE RISK EVALUATION IN PATIENT M.A., 63 YEARS OLD WITH HYPERTENSION AND NEPHROLITHIASIS SINCE FOUR YEARS

In all the geriatric patients enrolled in the study, one revealed that fixed-dose combination of Aml + Val + HCTZ 10/320/25 mg is very useful in reducing blood pressure and monitoring it in case of long-term administration, due to optimal pharmacokinetic profile of the three component drugs, as described for the first time by Coulhan and co-workers in 2009 [21].

Among the patients taken in the study, 36 (60%) were recurrent stone formers therefore they had a high urinary stone risk.

In the whole, the treatment with Aml + Val + HCTZ 10/320/25 mg reduced the urinary stone risk by lowering the main parameters which composed it, as following:

-urinary phosphorus (mg/day) - from 904 ± 32 at 612 ± 18 (at the end of the study);

-calciuria (mg/day) - from 256 ± 14 at 148 ± 28 (at the end of the study);

-oxaluria (mg/day) - from 34 ± 18 at 21 ± 16 (at the end of the study).

The participants were followed for the occurrence of a kidney stone event while maintaining continuous usage on their drug, but no calculus was reported.

In accordance with recent valuable researches undertaken in this scientific field, we tried to reveal and understand the comorbidity of patients with arterial hypertension and nephrolithiasis [22]. In this context, our results were in accordance with Fernández-Rodríguez and co-workers, who pointed out that in the elderly patients, the treatment with 25 mg/day of hydrochlorothiazide (from the combination of Aml + Val + HCTZ 10/320/25 mg) has a beneficial and prolonged efficacy in treatment of recurrences in patients with calcium oxalate and phosphate lithiasis [23].

Conclusions

Our study reveals that in the elderly patients with hypertension and nephrolithiasis as a comorbidity, thiazides - 25 mg/day of hydrochlorothiazide (from the combination of Aml + Val + HCTZ 10/320/25 mg) have a beneficial effect in order to control lithogenic factors and recurrences in patients with calcium phosphate lithiasis.

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