

ORIGINAL RESEARCH

To study the features of the use of phytotherapeutic drug *Herba Gnaphalii uliginosi* in combination with the main group of pharmacological drugs in the treatment of hypertension with concomitant angina

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The article looks into the spread of cardiovascular diseases in the elderly in Ukraine. It is noted that with the approach of old age with the development of various somatic and mental diseases there are changes in health, changes in the direction of life interests, and changes in social status (1). It is established that the combination of a group of drugs with a non-medicinal mixture of medicinal herbs gives a positive result in lowering blood pressure, improving heart rate, and clinical performance of the cardiovascular system (2). Deep dynamic changes - a new phenomenon that is characteristic of our century, have led to a significant “aging” of the population. The aging process largely explains the high percentage of morbidity and mortality (62.5%) from cardiovascular system diseases (3). Due to the accumulation of several diseases in old age, with a predominantly chronic course and constant exacerbation, the majority of elderly people are in increased demand for medical care. At present, more than half of the patients who see a therapist at the clinic are elderly and senile (4, 5).

Keywords: cardiovascular disease, hypertension, coronary heart disease, old age, medication, herbal tea

Introduction

Despite the current concept of treatment of heart disease, today the risk of serious cardiovascular complications remains high, and the progression of the disease continues despite optimal therapy. That is why today doctors face the problem of answering the question: “How to treat?.” The solution to this problem is formed by the accepted paradigm of treatment of patients of all ages, especially the elderly and senile (6). Therefore, in the treatment of the elderly, doctors must set a goal that can be achieved.

The main problems of drug treatment are related to:

- the need to prescribe more than one drug;
- the need for frequent long-term medication in connection with the chronic course of many diseases;

- disorders of pharmacodynamics and pharmacokinetics of drugs against the background of age-related involution changes in organs and systems;
- Violation of compliance - insufficient or incorrect implementation of the prescribed regimen of drug therapy.

Rational treatment of the elderly patient requires the achievement of mutual understanding between doctor and patient (7).

Important in the treatment of the elderly and senile is the timely detection of side effects of drug treatment. Therefore, today, more people are beginning to introduce a combination of drug therapy with phytotherapy, which prompted us to conduct original research.

Research elaborations

The research was conducted at the Cardiology Department of Cherkasy City Hospital N^o 1 (Ukraine) in the period from September 2021 to February 10, 2022. The main selection criteria were men and women aged 55–80 years (average 66.07 ± 1.20) who were diagnosed with coronary heart disease grade 2-3 angina, atherosclerotic cardiosclerosis, hypertension grade 2-3, myocardial infarction, atherosclerosis. Among those surveyed were 82 females and 46 males.

The study was conducted in compliance with the basic bioethical provisions of the Council of Europe Convention on Human Rights and Biomedicine (04.04.1997), the Helsinki Declaration of the World Medical Association on ethical principles of scientific medical research with human participation (1994–2008), and the Ministry of Health Of Ukraine N 690 dated September 23, 2009.

The examination protocol included measurement of blood pressure by auscultatory method Korotkov (micro life tonometer, BP AG1-30 Switzerland) heart rate, electrocardiogram (using a 2-channel portable electrocardiograph LN-1 in two leads V1-V5) before and after treatment with a group of drugs, biochemical analysis of blood and urine.

Results of the research and discussion

Diseases of the circulatory system rank first in prevalence and incidence, accounting for more than half of all deaths and a third of the causes of disability. To reduce or eliminate the most common forms of cardiovascular disease, including hypertension, and coronary heart disease, phytotherapeutic drugs are used (8).

Complaints of patients with intermittent prolonged headaches, dizziness, accompanied by tinnitus, weakness indicate a violation of microcirculation in the brain, associated with increased systemic blood pressure. This leads to compensatory narrowing of the vessels of the brain. Spasm of arterioles caused by neurogenic factors (adrenaline release and activation of the sympathetic system under stress) occurs in all organs, including the kidneys, which contributes to the activation of the renin angiotensin-aldosterone system, Na retention, and water retention, which leads to secondary reflex narrowing of arterioles to reduce excessive perfusion of organs, retention of Na + in vascular myocytes, and increase the sensitivity of the latter to pressors (2). All this eventually leads to sclerosis and hyalinosis of resistive vessels, a steady increase in peripheral resistance, which causes hypoxia and ischemia of organs, dysfunction, and the emergence of pain impulses (including from the heart). Increased blood flow to the heart

necessitates increased myocardial hypertrophy to ensure adequate vascular discharge during systole, while stroke volume increases. Compensatory hypertrophy occurs first, which can lead to a mismatch between cardiac activity and myocardial blood supply, followed by coronary heart disease and heart failure. Left ventricular hypertrophy was detected in the patient during an objective examination (palpation, percussion, auscultation) and confirmed by instrumental diagnostic methods (electro-, echocardiography). A systemic increase in blood pressure and compensatory narrowing of the arterioles leads to the vortex of blood flow, and damage to the endothelial layer of blood vessels, which causes the penetration of low-density lipoproteins and eventually leads to the development of atherosclerosis (9). This in turn threatens thromboembolism, aneurysms, rupture of blood vessel walls, and hemorrhages (especially severe intracranial bleeding). Coronary atherosclerosis leads to coronary heart disease and myocardial infarction. Hypoxia of organs and tissues causes reflex acceleration and deepening of respiration, accompanied by shortness of breath (1).

Based on the above complaints and medical history of patients, data from objective and instrumental examinations can be diagnosed (Diagnosis terminals): hypertension (Morbus hypertonic) in stage II (according to the classification based on the level and stability of blood pressure - stable increase in diastolic blood pressure not more than 115 mm Hg), heart failure, accompanied by shortness of breath and changes in heart muscle function (10).

Therefore, based on the above, drug treatment was prescribed, which was based on etiopathogenetic treatment (phytotherapy), as a basis for improving the general wellbeing of patients without any side effects. Today, the most common herbal medicine is *Herba Gnaphalii uliginosi* (11). It is an annual herbaceous, grayish-green, gray, or white plant. Stem from 5 to 30°cm tall, branched. Coots alternate, elongated linear, obtuse, narrowed to the base. Inflorescences consist of yellowish flowers in ovoid small baskets, which are densely packed in balls at the tips of shoots and surrounded, like rays, by leaves. The fruit is achene. It grows in gray forests, in floodplain meadows, in drying swamps, and as a weed in gardens and fields found throughout the European part of the European Union. The grass is harvested during flowering, sometimes with roots, dried in the open air or dryers at temperatures up to 40°C. The chemical composition of the grass is represented by flavonols (quercetin, kaempferol) and flavones (gnaphalosides A and B, 7-O-glucoside scotelearein). There are also tannins (4%), resins, carotenoids, phytosterols, and ascorbic acid. The lipophilic fraction contains carotenoids, and terpenoids.

Infusion and decoction have vasoconstrictive and antihypertensive effects and slow the heart rate (11; Figure 1).

An infusion of dried marshmallows was used for 10 days of inpatient treatment of patients. The cardiologist prescribed patients the main groups of drugs (such as antiadrenergic



FIGURE 1 | General view of the packaging of the drug used in the treatment of hypertension.

drugs clonidine or catapressan, methyl dopa, reserpine), peripheral antiadrenergic drugs— α -receptor antagonists (phentolamine, prazosin), antagonists of heart β -hollan antagonists. α and β -receptor antagonists (labetalol). The use of ganglioblockers (benzohexonium, pentamidine) disrupts the transmission of nerve impulses through the peripheral ganglia, which leads to a decrease in blood pressure. Combination preparations containing reserpine, saluretic, potassium, or hydralazine (Adelphi, Adelphi-Esidrix K, cristipine, birch), which cause a gradual decrease in blood pressure, as well as an infusion in a dosage of 1/3 cup 30 min before taking are also used. Food 2 times a day.

From **Figure 2** shows that already on the 3rd day of complex treatment of patients with hypertension with concomitant angina leads to normalization of systolic and diastolic pressure, and on the 14th day of treatment, even a decrease in diastolic pressure compared to the first day of treatment. Significance of the difference $p < 0.05$. Thus, systolic blood pressure in comparison with the first day of treatment decreases in the range from 14.03 to 29.75 mm Hg during the treatment period.

Diastolic blood pressure varies from 7.5 to 17.73 mm Hg over 10 days.

At this time, patients showed improvement in general well-being, reduction of complaints of angina, dull, burning pain in the heart, improved mood, and disappearance of headache.

The long-term prognosis in patients with heart failure is unfavorable: over the past 4 years, patient mortality is 50%.

The key mechanism of chronic heart failure is the activation of neurohumoral systems, in particular sympathoadrenal, in response to reduced cardiac output.

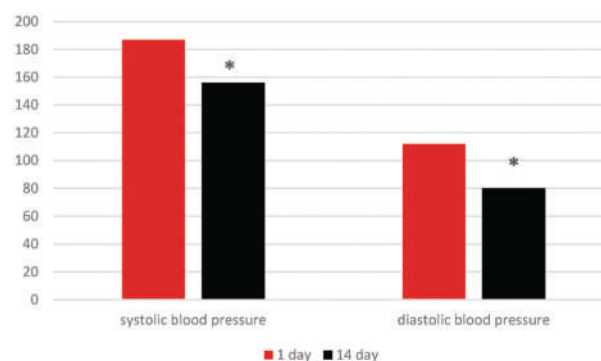


FIGURE 2 | Dynamics of distribution of systolic and diastolic arterial pressures during 14 days of treatment of patients with hypertension with the use of phytotherapeutic preparation Dried flowers of marshmallow (Herba Gnaphalii uliginous).

In patients with chronic heart failure, elevated plasma norepinephrine levels correlate with an unfavorable prognosis. Beta-blockers are recommended for the treatment of all patients with unstable, moderate, and severe heart failure (HF) due to ischemic or non-ischemic cardiomyopathy and left ventricular ejection fraction (EF) receiving standard therapy, including diuretics and inhibitors, when they are contraindicated. The use of betablockers in patients with chronic heart failure leads to slower progression and even reversal of cardiac remodeling.

Currently, the main goal in the treatment of hypertension (H) is also the correction of target organs (heart, blood vessels), which includes the reverse positive way of modeling the cardiovascular system (12).

β -blockers are the main drugs in antihypertensive therapy. But they do not promote remodulation of blood vessels.

Nubiles are the new most selective beta-blocker with a selectivity index of 288 (Bisoprolol-26).

The composition of the drug: the active substance-1 tablet contains nebivolol hydrochloride 5.45 mg, which is equivalent to 5 mg of nebivolol; Excipients - lactose monohydrate, corn starch, sodium salt of “crosslinked” carboxymethylcellulose, hydroxymethyl cellulose 15 mPa-s, high-dispersion silicon dioxide, polysorbate 80, microcrystalline cellulose, magnesium stearate. Dosage form-tablets.

Pharmacotherapeutic group: β -adrenoceptor blockers. Pharmacological properties-Nebivolol consists of two enantiomers: SRRR-nebivolol (D-nebivolol) and RSS-nebivolol (L-nebivolol). It combines two pharmacological properties:

- due to the D-enantiomer, nebivolol is a competitive and selective blocker of β_1 -adrenoceptors;

Thanks to the L-enetomir, it has “soft” vasodilatory properties due to the metabolic interaction with L-arginine/nitric oxide (NO).

In the treatment of chronic heart failure with the drug “Nebilet” dosing should begin with a gradual increase in dose

according to the following scheme: the initial dose of 2.5 mg nebivolol 1 time per day may be, depending on tolerability, be increased to 5–10 mg nebivolol 1 once a day. The maximum recommended dose is 10 mg. In patients with severe HF treated with diuretics, there may be a significant decrease in blood pressure after the first dose of nebivolol, as well as after an increased dose of the drug. Therefore, such patients should be monitored by a physician for approximately 2 h after taking the drug, to reduce the risk of uncontrolled antihypertensive reactions (13).

Twenty-five patients with hypertension with signs of chronic heart failure were monitored. Including 14 men and 11 women aged 62 to 78 years (mean age was 64.21 ± 1.09).

Based on patient complaints of periodic headaches lasting several days, dizziness accompanying headaches, tinnitus, pain in the projection of the apex of the heart (cardialgia), which are prickly and occur with physical or emotional overload, palpitations (palpitation cordis) there was a significant relief after taking sedatives and antihypertensives.

According to the objective examination (stable increase in blood pressure within 190/110, heart rate 96 beats/min, pulse in the radial arteries is intense, hard, full, palpatory apical shock is shifted to the sixth intercostal space up to 1 cm outside the left midclavicular line, high resistant, diffuse, percussive relative dullness of the left border of the heart is shifted to the left of the midclavicular line by 1 cm; auscultatory I tone at the apex of the heart is weakened, above the aorta, there is an accent II tone) with recorded signs of chronic heart failure.

In the process of individual dose selection of Nebilet, a positive antihypertensive effect was registered in inpatients.

The dose of Nebilet was effective in 10 people and was 5 mg/day; in 9 people the dose was 10 mg/day, and in 6 people during day hospital treatment the dose was reduced to 2.5 mg/day.

In the 1st week of treatment, there was a partial decrease in heart rate. Thus, the heart rate (HR) decreased from 86.21 ± 1.23 to 63.52 ± 1.90 ($p < 0.01$). Starting from the 1st week, a positive and relatively stable hypertensive effect was observed. Compared with the beginning of treatment, systolic blood pressure (SBP) decreased from 163.25 ± 2.76 to 130.25 ± 1.59 mm Hg, in turn, diastolic blood pressure (DBP) decreased from 83.25 ± 1.009 to $79, 53 \pm 1,009$ mm Hg ($p < 0.01$).

Against the background of therapy, the subjective condition of patients significantly improved, headache, prickly pain in the heart area, dizziness, and shortness of breath during exercise decreased.

To date, it has been found that the use of β -blockers in medical practice for the treatment of heart failure is appropriate. The results of many observations indicate a positive effect on the performance of the cardiovascular system, thereby reducing mortality and hospitalization.

The drug “Corvasan” has the following pharmacotherapeutic properties such as antihypertensive, anti-ischemic, and antiarrhythmic effects.

The composition of the drug: the active substance one tablet contains carvedilol 12.5 or 25 mg;

Excipients: potato starch, granules-70, microcrystalline cellulose, low molecular weight polyvinylpyrrolidone, talc, calcium stearate.

Pharmacological properties. Carvedilol is a combined α -1 and selective β -adrenoceptor blocker. Causes dilation of peripheral blood vessels and reduces blood flow resistance. Has an antioxidant effect, reduces left ventricular hypertrophy, and improves the diastolic function of the left ventricle (cardioprotective effect).

Has an anti-ischemic and anti-anginal effect. Does not show an adverse effect on lipid and glucose metabolism, does not affect the level of electrolytes in blood plasma, and does not change peripheral blood flow.

It is quickly absorbed after the reception. The maximum concentration in blood plasma is reached in 1–2 h. Bioavailability is increased in patients with liver disease and the elderly (up to 50%).

Concomitant use of carvedilol with food slows down the absorption of the drug but does not reduce its volume. A Total 98% of carvedilol is bound to plasma proteins. Duration of action - more than 15 h. Excreted mainly in bile and feces as metabolites.

The use of β -blockers in older age groups differs from that recommended in the middle-aged group, due to age-related involuntional features of the senile organism as well as pharmacokinetics and pharmacodynamics of drugs (14).

That is why the recommended use of the drug “Corvasan” in the elderly and senile should be taken at a dose of 50 mg per day. Moreover, the initial dose should be 3.125 mg with a subsequent increase to the specified limit (within 2–3 weeks). The duration of the drug is not limited.

The group of patients admitted to the hospital of different ages (average 52.16 ± 2.9) and sex categories, primarily differed from other elderly patients with chronic congestive heart failure, which usually develops in the late and distant periods of extensive and recurrent myocardial infarction. Quite often it occurs if myocardial infarction is complicated by a heart aneurysm or persistent arrhythmias, especially atrial fibrillation. Patients complained of sharp, sudden pain in the chest, the pain spread to the back, especially to the lower back, abdomen, groin, and lower extremities.

During the outpatient examination, we found: leukocytosis, and increased content of α -globulins. Quite often patients also complained of fever. Palpation revealed pathological pulsation of the anterior chest wall, especially in the third or fourth intercostal space to the left of the sternum. Auscultatory deafness of heart sounds, often systolic murmur due to the development of relative mitral valve insufficiency due to myogenic dilatation, as well as papillary muscle damage were heard. The so-called frozen

electrocardiogram (ECG) is characteristic - a long dome-shifted ST-segment in combination with a negative T wave.

An ECG examination was performed on each elderly and senile patient before the initial administration of the drug. The results of the electrocardiographic examination are presented below and showed: sinus rhythm, heart rate - 96 per minute, voltage is preserved, the electrical axis of the heart is deflected to the left (α -16°); signs of left ventricular hypertrophy: increased amplitude R in the leads I, II, V₅, V₆, aVL, R_I > R_{II} > R_{III}, increased amplitude R in leads II, III, V_I, V_{II}, aVF. Increased amplitude and duration of the QRS complex. The T tooth is flattened in the leads I, V₅, V₆, aVL, and the ST segment is slightly lowered relative to the isoline (such data were found in every second patient).

The following pathological picture was observed in several patients: sinus rhythm with heart rate - 63 (62–67) per minute, R-R fluctuations of 7%. Voltage saved. The electrical axis is deflected by 49°. Severe left ventricular hypertrophy with signs of systolic overload and moderate right ventricular dilatation. Incomplete blockade of the right leg of the His bundle. R-R_{II} 0,958; P-Q_{II}0,168; Q-T_{II}0,372; P_{II}0,112; QRS_{II} 0,092.

The initial dose of the drug for patients of all ages of the examined groups and physique was in the range of 3.125 mg twice a day, followed by a gradual increase over 3–4 weeks to 50 mg. Because the patients were on 14^o day treatment, they came under the supervision of a local cardiologist at home to take the drug for a long time and improve their health.

After 7 days of taking the drug in most patients, we observed: first of all - a decrease in the use of long-acting anti-anginal drugs, reducing the need for nitroglycerin.

The data in **Figure 3** indicate that there was a significant decrease in heart rate before and after treatment with the drug (14^o day period, followed by a long prolongation). Heart rate in the first 7 days of treatment decreased from 96.04 ± 2.16 to 78.46 ± 1.62 , then on day 14 (day of discharge), this figure was 62.91 ± 4.23 ($p < 0.01$).

It should be noted that significant changes were also observed in the repeated ECG study: voltage saved, heart rate 62, decrease in ST-segment by $0.32 \pm 0.04^{\circ}$ mV, decrease in the amplitude and duration of the QRS complex R-R oscillations by 7%.

During the next 7 days of treatment, there was an increase in exercise tolerance (because each patient was prescribed exercise at the beginning of treatment under the supervision of a physiotherapist), reduced incidence of destabilization of coronary heart disease (CHD), improved morphofunctional and hemorheological parameters of SS.

The prevalence of hypertension in our city shows that most patients have 1 and 2 functional stages of the disease.

Today, angiotensin-converting enzyme (ACE) inhibitors are most often prescribed (3).

Fosinopril differs from other ACE inhibitors by its chemical structure and pharmacokinetics. Unlike other

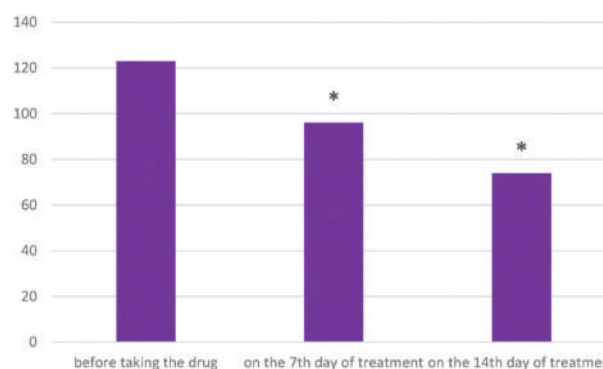


FIGURE 3 | Heart rate (HR) before and after taking the drug “Corvazan” in patients with myocardial infarction.

drugs, its metabolic transformation occurs not only in the liver but also in the mucous membrane of the gastrointestinal tract, as well as in the kidneys and bloodstream. The kidneys excrete 44–50% of the drug, and the intestine 46–50% (15). The half-life of fosinopril in blood plasma is 12–15 h, which causes the long-term antihypertensive effect of the drug, which allows you to prescribe it once a day.

It should be noted that due to the high lipophilicity of the drug, it easily penetrates all organs and tissues of organisms, thereby reducing the activity of not only circulating ACE but also tissue (heart, lungs, kidneys, brain), which is extremely important clinically (16). Due to its lipophilicity, fosinopril can eliminate ultra-high activation not only of the circulating but also of the tissue renin-angiotensin-aldosterone system.

Pharmacological composition of the drug: active substance-1 tablet contains 10 or 20 mg of fosinopril sodium.

Excipient lactose anhydrous, microcrystalline cellulose, crospovidone, ethyl alcohol, povidone, sodium stearyl fumarate.

Fosinopril, like any ACE inhibitor, can be combined with other antihypertensive drugs. Thus, the combination of Fosinopril with HCT (hydrochlorothiazide) allows in many cases to achieve more effective blood pressure control than with monotherapy (17).

Fosinopril has several unique pharmacological properties that allow us to consider this drug as one of the most effective and safe representatives of this class for the treatment of hypertension.

Studies have been performed on patients with moderate to severe hypertension. Provided that at the end of the 7th period of withdrawal of all antihypertensive drugs, the average value of blood pressure, measured in the morning in a sitting position, was above 140/90 mm Hg. A combination of Fosinopril and HCT was prescribed as therapy. The initial dose was 10 mg Fosinopril and 6.25 mg HCT. If therapy was ineffective, the dose was doubled and, if necessary, increased to a maximum of 40 and 25 mg per day, respectively.

Already on the 8th day of treatment, there was a significant decrease in the levels of SAT, DBP, and heart rate, which

helped many patients to achieve the target blood pressure. At the end of the 2nd week of the study, the rate of CAT was -30.25 , DBP -14.08 mm Hg ($p < 0.001$ compared to baseline). Reduction of heart rate by 16.89 beats/min (the significance of the difference is $p < 0.05$). Blood pressure continued to decline throughout the treatment period. There was a significant decrease in blood pressure, as well as a decrease in the average daily value of SAT and DBP at the end of the study was 16.25 and 7.01 mm Hg, respectively. The average daily heart rate did not change significantly.

The average daily dose of Fosinopril at the end of treatment was 18.8 ± 1.0 mg. At the end of the treatment period, the predominant number of patients received hydrochlorothiazide (HCT) at a dose of 12.5 mg—67, 28.9% received a daily dose of 25 mg and only 3.2% of patients received 6.25 mg of HCTZ per day. The average daily dose of HCT was 13.1 ± 0.9 mg.

During the treatment period, no significant changes in the parameters of general, biochemical blood, and urine tests were detected.

It is necessary to pay attention to the lack of reliable dynamics of the level of potassium and sodium in blood serum.

Adverse reactions were observed in only 5.6% of patients, in the form of dry cough (which decreased with decreasing dose), headache, and dizziness. The drug was not canceled in any patient.

Thus, the combination of Fosinopril 10–40 mg and HCT 6.25–25 mg in patients with severe and severe hypertension for 2 weeks of treatment showed a pronounced antihypertensive effect with good tolerability and single administration.

Conclusion

Based on the research, we came to the following conclusions:

1. The use in the practice of phytotherapeutic preparation of infusion of dried marshmallow (*Herba Gnaphalii uliginos*) is recommended as one of the options to reduce heart disease in the elderly and senile.
2. The drug “Nebilet” is recommended for the treatment of elderly patients in order to reduce mortality and prevent the progression of heart failure, and cardiovascular complications.
3. Patients with coronary heart disease of older age groups are recommended the drug “Corvazan” at a dose of 50 mg per day in two doses as a drug

that improves the performance of the cardiovascular system after myocardial infarction.

4. The drug “Monopril” promotes a pronounced antihypertensive effect and is well tolerated by patients. Therefore, this drug should be widely used to optimize blood pressure.

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