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ЗАСТОСУВАННЯ КОМБІНОВАНОЇ ТЕРАПІЇ У ПАЦІЄНТІВ З АГ У ПОЄДНАННІ З ХОЗЛ

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APPLICATION OF COMBINED THERAPY IN HOSPITAL PATIENTS WITH ARTERIAL HYPERTENSION AND COMORBID CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Анотація. Сучасним напрямком розвитку клініки внутрішніх хвороб і сімейної медицини є вивчення коморбідних станів, серед яких у практиці лікаря значне місце займає артеріальна гіпертензія та хронічне обструктивне захворювання легень. Коливання артеріального тиску погіршує прогноз, а труднощі при виборі лікування залишаються серйозною проблемою при веденні пацієнтів з артеріальною гіпертензією та хронічним обструктивним захворюванням легень. Тому необхідною є оптимізація ведення пацієнтів з поєднаною патологією на всіх рівнях медичної допомоги.

Summary. The modern direction of development of internal diseases clinic and family medicine is a studying of comorbid conditions, among which in the doctor's practice the significant part takes arterial hypertension and chronic obstructive pulmonary disease. Oscillation blood pressure worsen the prognosis, and difficulties in choosing treatment remain a serious problem in the management of patients with arterial hypertension and chronic obstructive pulmonary disease. Therefore, it is necessary to optimize the management of patients with multiple pathologies at all levels of care.

Ключові слова: артеріальна гіпертензія, хронічне обструктивне захворювання легень, добове моніторування артеріального тиску, валсартан, амлодипін, умеклідініум бромід, вілантерол.

Key words: arterial hypertension, chronic obstructive pulmonary disease, ambulatory blood pressure monitoring, valsartan, amlodipine, umeclidinium bromide, vilanterol.

Nowadays, the incidence of hospitalizations for the combined course of cardiovascular disease (CVD) and chronic obstructive pulmonary disease (COPD) is increasing. In Ukraine, about 22.3 million people suffer from circulatory system diseases, accounting for 52.4% of the total population [8]. Arterial hypertension (AH) among comorbid conditions, which occurs in 35% of cases, occupies a significant place. The prevalence of COPD is 10.1% in people over 40 years, and is more prevalent in smokers and the elderly. By 2030, COPD is expected to be the fourth leading cause of death

worldwide and the third leading cause among middle-income countries [1].

Difficulties in the choice of treatment for patients with arterial hypertension in combination with COPD remain a serious problem, since the combination of these diseases leads to significant inter-burden. The doctor faces the question of prescribing effective therapy for hypertension and COPD, which should be safe in conditions of comorbidity.

In the treatment of patients with arterial hypertension, the basic conditions are the provision of ambulatory blood pressure monitoring (ABPM), normalization of the BP's daily profile, the absence of a negative impact on the tone of the bronchi and their patency, a positive effect on the hemodynamics of the microvascular, cardio- and angioprotective effects [7].

According to the ECS Guidelines, preference should be given to combinations of anti-RAAS and **dihydropyridines** calcium channel blockers (CCBs) [4,9]. Numerous randomized controlled trials have shown that monotherapy is not effective in patients with comorbid pathology, that confirmed the need for combination therapy [7].

According to the literature, on the background of valsartan therapy is normalization of the daily profile of blood pressure, reducing the variability of blood pressure in the absence of influence on the bronchial patency of patients [7]. Dihydropyridine CCBs, in turn, are the drugs of choice because they contribute to the reduction of bronchial hyperreactivity and have a bronchodilatory effect. In addition, according to the meta-analysis, CCB was detected the dose dependence effect, and the used of higher doses was associated with significantly less variability in systolic BP (SBP) [9].

The use of the method of ABPM makes it possible to objectively assess its true level during the day and diagnose arterial hypertension at an early stage, which is of great importance for the diagnosis of the combination of these conditions. Prevalence of different phenotypes characterized by insufficient decrease and often increase in blood pressure at night ("non-dippers" and "night-peakers"), in patients with hypertension in combination with COPD is 4.7 times higher than in patients with hypertension without COPD [7].

The basis of pharmacotherapy COPD is the use of long-acting bronchodilators: long-acting muscarinic antagonists (LAMA) and long-acting β2-agonists (LABA), as they improve lung function, reduce shortness of breath, increase physical performance and prevent further exacerbation [2]. Combination of bronchodilatators of different classes leads to improved efficiency with fewer side effects compared to increased doses of single-component therapy. No adverse effects on cardiovascular system have been identified during the ABPM and daily EKG monitoring in patients with hypertension and COPD on the background of long-term therapy umeclidinium bromide with vilanterol, which allows the use of this combination to treat comorbid pathology [3]. So the use of LAMA and LABA in fixed-dose combination inhalation is a modern treatment option for COPD patients and recommended by GOLD-2019 [6].

THE AIM OF THE STUDY. To evaluate the effect of combinations of valsartan with amlodipine and umeclidinium bromide with vilanterol in patients with arterial hypertension in combination with chronic obstructive pulmonary disease.

MATERIALS AND METHODS OF RESEARCH. The study included 60 patients with arterial hypertension in combination with COPD, including 54 men and 6 women, aged 59 ± 7.2 years, who received a combination of valsartan (an anti-RAAS) with amlodipine (a calcium channel blocker) and umeclidinium bromide (long-acting muscarinic receptor antagonist) with vilanterol (selective long-acting β2-adrenergic receptor agonist) for 6 months.

All patients were examined and clinically monitored at the Kryvyi Rih City Clinical Hospital №2 for the period 2016-2019. The stage and grade of hypertension were determined according to the recommendations of the European Society of Cardiologists (2018) and the Ukrainian Association of Cardiologists (2018) [4,10].

Criteria for inclusion in the study: primary (essential) hypertension, COPD, voluntary consent to participate in the study according to the 2000 Helsinki Declaration.

Exclusion criteria are secondary AH, ischaemic heart disease, heart failure above grade I according to the All-Ukrainian Association of Cardiologists (2017) and II Class according to New York Heart Association (NYHA), cerebral circulation disorders, chronic kidney disease, diabetes mellitus.

The severity of COPD was established in accordance with the Ministry of Health Order of Ukraine No. 555 of June 27, 2013 and the GOLD 2019 Guidelines [5,6]. The doses of the drugs were established according to the severity of the manifestations of hypertension and COPD, as - valsartan 80-160mg/day, amlodipine 5-10 mg/day, umeclidinium bromide with vilanterol - 55/22 mg/day.

Research methods included general clinical examination, electrocardiography at rest (ECG), ABPM, spirometry.

The following indicators were analyzed: 24-hour average, daytime average and night-time average values of SBP, diastolic (DBP), heart rate, variability of SBP and DBP, with the degree of reduction of SBP at night characterized the daily profile of BP, patients with a sufficient decrease (by 10–20%) were classified as dippers, with insufficient reduction (<10%) - non-dippers, over-dipper - with excessive reduction (>20%), in the presence of nocturnal hypertension patients were enrolled to night-peakers (>0%). The function of external respiration characterized by forced expiratory volume in the first one second (FEV_1), forced vital capacity of the lungs (FVC), the ratio of forced expiratory volume in the first second to the forced vital capacity of the lungs (FEV_1/FVC).

Mathematical and statistical analysis of the results of the study was performed using the licensed program STATISTICA (version 6.1), serial number

AGAR 909 E415822FA using determination of mean values (M), standard deviation (SD), errors of mean value (m), (M±SD), and the interquartile range medians (Me [25–75%]). Significant differences were assumed to be $p<0.05$.

RESEARCH RESULTS

Stage I hypertension was detected in 5 (8.3%) patients, and II – In 55 (91.7%) patients. 1 grade BP was diagnosed in 10 (16.7%) patients, 2 – in 41 (68.3%), 3 – in 9 (15%). Grade 1 COPD was detected in 3 patients (5%), 2 – in 25 (41.7%), 3 – in 19 (31.7%), 4 – in 13 (21.6%).

Clinical group A - 1 (1%) patient, B - in 26 (43,3%) patients, C - in 11 (18,3%), D - in 22 (36,7%). Among the smokers surveyed, 29 (48.3%) patients were identified, and smoking duration was 14.5 [5;28.5] patches. The duration of hypertension was on average 10 [7;13] years, the duration of COPD – was 10 [8;14] years. The number of exacerbations with hypertension is on average 2 [1;3] times, and COPD - 2 [2;3] times. CAT - 21 [17;28] points, mMRC - 3 [2;4] points. The clinical characteristics of the group are shown in table. 1. In the course of ABPM, patients with hypertension combined with COPD revealed a steady increase in blood pressure, which 24-hour averaged for SBP 165.1 [150.4;180.6] mmHg and for DBP 103.2 [94.6;111.2] mmHg, which corresponds to the level of moderate hypertension (2 grade), and indicates a significant excess of the average daily BP values in this group. The daytime average SBP in the group of patients was 160.3 [140.6;180.3] mmHg, DBP - 105.6 [93.3;117.5] mmHg. The night-time average SBP was 165.7 [155.6;175.5] mmHg, and the DBP was 100.3 [95.8;105.7] mmHg in accordance.

Table 1

GENERAL CHARACTERISTICS OF PATIENTS

PARAMETERS	
Stage AH, n (%)	
I	5 (8,3%)
II	55 (91,7%)
Grade AH, n (%)	
1	10 (16,7%)
2	41 (68,3%)
3	9 (15%)
Grade COPD, n (%)	
1	3 (5%)
2	25 (41,7%)
3	19 (31,7%)
4	13 (21,6%)
Clinical group COPD, n (%)	
A	1 (1,6%)
B	26 (43,3%)
C	11 (18,3%)
D	22 (36,7%)
Age, y	59±7,2
Sex, men/women (n)	54/6
Smoking duration, n	14,5 [5;28,5]
Current smoker, n (%)	29 (48,3%)
Duration of hypertension, y	10 [7;13]
Duration of COPD, y	10 [8;14]
Exacerbations with hypertension per year, (n)	2 [1;3]
Exacerbations with COPD per year, (n)	2 [2;3]
CAT, b.	21 [17;28]
mMRC, b.	3 [2;4]

In addition, the mean daily (24-hour) index (DI) SBP in the patient group was 16.4% [14.2;18.6]% and DI DBP 11,0 [9,2;13,2]%, which indicates the prevalence of 24-hour phenotypes "non-dippers" and "night-peakers" on the background of increase of heart rate 83 [76;90]/min. Insufficient nocturnal decrease in blood pressure is an adverse sign for the prognosis because it leads to damage to the target organs. This view was confirmed by a significantly higher time index (IR) for both SBP and DBP in patients in this group and variability in BP.

High rates of hemodynamic daily load - "pressure load", insufficient night reduction of blood pressure, increase of IT (SBP 74,8 [69,1;80,2]%, DBP 66,6 [59,7;73,9]% were established) and the area index (AI) (SBP 34.7 [32.1;38.5]%, DBP 21.6 [18.9;23.4]%) of hypertension, which is a feature of the daily profile of BP in patients with COPD and hypertension, which indicate the possibility of early development of HF and significantly increase the progression of combined pathology and the risk of complications.

COPD is accompanied by persistent bronchial obstruction and hypoxia, which is most pronounced at night and in the morning. Formation of a daily profile of AH depends largely on the state of sympathoadrenal and renin-angiotensin-aldosterone systems, whose activity is enhanced with the combination of AH and COPD. Indicators of external respiration function

(ERF) before the appointment of complex therapy were: FEV_1 – 40,5 [27,7;58,3]%, FVC – 59,3 [47,4;68,1]%, FEV_1/FVC – 0,58 [0,48;0,70].

Table 2

COMPARATIVE CHARACTERISTICS OF INDICATORS ABPM BEFORE AND AFTER TREATMENT

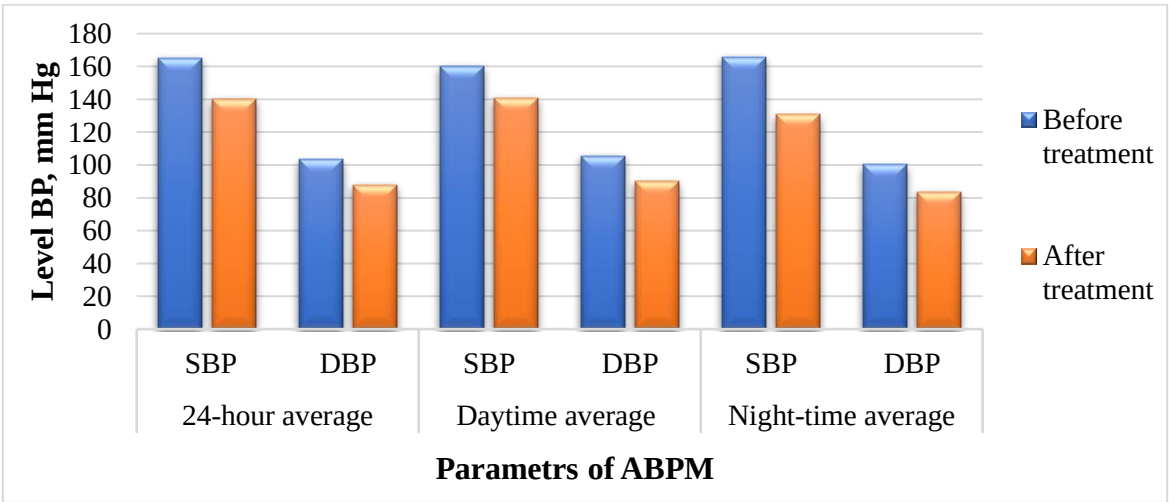
Parameters	Before treatment	After treatment
24-hour average, mm Hg SBP DBP	 165,1 [150,4;180,6] 103,2 [94,6;111,2]	 140,3 [120,8;154,6]* 87,7 [80,3;93,4]*
Daytime average, mm Hg SBP DBP	 160,3 [140,6;180,3] 105,6 [93,3;117,5]	 140,7 [130,6;160,4]* 90,1 [85,6;95,8]*
Night-time, mm Hg SBP DBP	 165,7 [155,6;175,5] 100,3 [95,8;105,7]	 130,7 [120,5;150,4]* 83,4 [75,3;90,2]*
FEV_1, %	40,5 [27,7;58,3]	46,7 [33,3;64,8]*
FVC, %	59,3 [47,4;68,1]	67,4 [50,3;70,2]*
FEV_1/FVC	0,58 [0,48;0,70]	0,64 [0,53;0,73]*
Respiration frequency, min.	21,5 [20;23,5]	16 [14;17]*
Heart retractions frequency, min.	83 [76;90]	76 [70;82]

*p<0,05

According to the ABPM, an analysis of the antihypertensive effect of valsartan with amlodipine (Table 2) showed a likely stable decrease in SBP and DBP and heart rate. The 24-hour average SBP decreased by 15%, the DBP - by 15.1%, respectively. The daytime average after treatment decreased by 12.2%, the DBP - by 14.6%. The average night-time SBP decreased by 21.1%, the DBP - by 16.8% (Pic. 1). The variability of SBP decreased by 30.1%, the DBP - by 67.0%. IT of SBP decreased by 55.9%, of DBP - by 41.1%, respectively. In turn, the IT of SBP decreased by 56.2%, the state-owned enterprise - by 57.4%. RF decreased by 25%. The HR decreased by 8.4%.

It should be noted that at the end of the observation period, 52 (86.6%) patients reached the target blood pressure level. When performing spirometry after complex treatment of umeclidinium bromide with vilanterol, the following values of external respiration function were obtained: FEV_1 - 46.7 [33.3;64.8]%, FVC - 67.4 [50.3;70.2]%, FEV_1/FVC - 0.64 [0.53;0.73]. Valsartan has a good dose-dependent antihypertensive effect and does not affect the perfusion-ventilation ratio, amlodipine has a vasodilatating effect on small blood vessels.

The normalization of ABPM indicators and the correction of pathological types of daily curves are statistically and clinically confirmed by reducing the amount of hypertension in patients with an increase or without decrease in blood pressure at night. In addition, complex treatment was well tolerated and did not lead to side effects requiring drug withdrawal.



Pic. 1. Comparative characteristics of indicators ABPM before and after treatment

Conclusions. In patients with hypertension combined with chronic obstructive pulmonary disease, the phenotypes of ambulatory blood pressure monitoring were dominated by non-dippers (38%) and night-peakers (26%). A comprehensive treatment approach is recommended, including the proposed combination of valsartan with amlodipine and umeclidinium bromide with vilanterol, which provides

a long-term antihypertensive effect and is safe in this category of patients.

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STRUCTURAL ORGANIZATION OF RAT HEPATIC CELLS AND THEIR CORRECTION WITH CRYOPRESERVED PLACENTA IN EXPERIMENTAL PERITONITIS

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СТРУКТУРНА ОРГАНІЗАЦІЯ КЛІТИН ПЕЧІНКИ ЩУРІВ ТА ЇХ КОРЕКЦІЯ КРІОКОНСЕРВОВАНОЮ ПЛАЦЕНТОЮ НА ТЛІ ЕКСПЕРИМЕНТАЛЬНОГО ПЕРИТОНІТУ

Summary. Currently, cellular and tissue therapy is widely used in treatment of various diseases. The specific state of hepatocytes has been studied histologically and electron-microscopically in simulated aseptic inflammation of the rats' abdominal wall followed by correction with transplantation of cryopreserved placenta within the period from day1 to day 30. Histologically, mainly dystrophic and destructive alterations of the liver cells have been detected during inflammation from day 1 to day 14, which were the same as before treatment. A recovery of the shape and structure of hepatocytes, blood supply and restoration of their functions started on day 14 of the experiment.

However, the findings of the electron microscopic study of the liver specimens in the first three days showed positive changes, manifested by the reactive state of the ultrastructure of hepatocytes and hemocapillaries, which improved in the mid-term time (day 5, 7) of the experiment and the structure of the sinusoid hemocapillaries and hepatocytes came to normal at the late terms (day 21, 30).

Анотація. В даний час для лікування різних захворювань організму все частіше застосовується клітинна і тканинна терапія. На експериментальній моделі асептичного запалення тканин черевної стінки щурів і корекції запалення трансплантацією кріоконсервованої плаценти були вивчені гістологічно і електронно-мікроскопічно особливості стану гепатоцитів в період з 1 до 30 діб. На тлі запалення з 1 до 14