Received: 28 February 2023 / Accepted: 28 May 2023 / Published online: 30 June 2023

DOI 10.34689/SH.2023.25.3.014

UDK 615.03:616.61

COMBINATION PHARMACOTHERAPY AS A RISK FACTOR FOR THE INCIDENCE OF RENAL FAILURE IN THE ELDERLY

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Summary

Introduction: Safety issues of drug combinations (DC) are always in the focus of attention of physicians, and special attention is required for elderly patients. Especially this problem relevant in recent years due to the increased level of polypragmasy in comorbid patients receiving drug therapy for the treatment of several diseases. It is possible to predict and prevent adverse effects of drug combinations, if to know the mechanisms of drug interactions.

Aim: To determine the risk factors of complications arterial hypertension pharmacotherapy in the combined use of antihypertensive and antiagregant drugs in the elderly.

Materials and methods: The study design was a single-center randomized prospective clinical trial. A total 343 patients who were followed up on an outpatient and inpatient basis for more than 3 years (mean follow-up period 4.1±1.0 years) were included in the study. Of these, 209 were women and 134 were men. There were 236 patients in the age group 66-70 years (68.8%), and 107 patients (31.2%) were older than 70 years (up to 80 years at the beginning of the study). A comparison of outcomes categorized into 2 groups - vascular and renal complications - was performed to determine the main outcomes. The endpoints of the study were: development of renal insufficiency II stage, patient death from any cause; development of acute coronary or cerebral circulatory failure.

Results: During the analysis of data obtained during an average of 4.1±1.0 years, 104 cases of CRI II stage development were identified. Co-administration of ACE inhibitors with antiaggregant drug was accompanied by statistically significant increase in the incidence of CRI II stage (incidence ratio 1.31 with 95% CI from 1.12 to 1.53).

Conclusion: Thus, the use in clinical practice for a large population of patients with cardiovascular diseases combinations of ACE inhibitors with NSAIDs significantly increase the risk of renal failure. Particular caution in the use of such a combination is required in risk groups: in elderly patients, with concomitant CKD, and comorbid conditions. In case of use of NSAIDs in patients receiving ACE inhibitors, monitoring of renal function parameters is required.

Key words: *arterial hypertension, pharmacotherapy, drug interactions, renal failure, elderly age.*

Аннотация

КОМБИНИРОВАННАЯ ФАРМАКОТЕРАПИЯ КАК ФАКТОР РИСКА РАЗВИТИЯ ПОЧЕЧНОЙ НЕДОСТАТОЧНОСТИ У ЛИЦ СТАРШЕЙ ВОЗРАСТНОЙ ГРУППЫ

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Введение: Вопросы безопасности комбинаций лекарственных средств (ЛС) постоянно находятся в центре внимания врачей, особенного внимания требуют пациенты старшей возрастной группы. Эта проблема особенно актуальна в последние годы в связи с возросшим уровнем полипрагмазии коморбидных пациентов, получающих лекарственную терапию для лечения нескольких заболеваний. Предсказать и предупредить неблагоприятные последствия комбинации ЛС возможно, если знать механизмы лекарственного взаимодействия.

Цель: определить факторы риска осложнений фармакотерапии АГ при сочетанном использовании антигипертензивных и антиагрегантных препаратов у лиц старшей возрастной группы.

Материалы и методы: Дизайн исследования – одноцентровое рандомизированное проспективное клиническое исследование. Всего в исследование включены 343 пациента, наблюдавшихся амбулаторно и в условиях стационара в течение более 3 лет (средний срок наблюдения 4,1±1,0 года). Из них женщин было 209, мужчин – 134. В возрастной группе 66-70 лет находилось 236 пациентов (68,8%), старше 70 лет (до 80 лет на момент начала исследования) – 107 (31,2%). Для определения основных результатов проведено сравнение исходов, распределенных на 2 группы – сосудистые и почечные осложнения. Конечными точками исследования являлись: развитие почечной недостаточности II ст, смерть пациента от любой причины; развитие острого нарушения коронарного или церебрального кровообращения.

Результаты исследования. В ходе выполнения анализа данных, полученных в течение в среднем 4,1±1,0 года, было выявлено 104 случая развития ХПН II ст. Сочетанный прием ИАПФ с антиагрегантным препаратом сопровождался статистически значимым увеличением частоты развития ХПН II ст. (отношения частоты 1,31 при 95% ДИ от 1,12 до 1,53).

Выводы: Таким образом, использование в клинической практике для большой популяции пациентов с сердечно-сосудистыми заболеваниями комбинаций иАПФ с препаратами НПВС значимо повышают риск развития почечной недостаточности. Особая осторожность применения такой комбинации требуется в группах риска: у пожилых пациентов, при сопутствующей ХБП, и коморбидных состояниях. В случае применения препаратов НПВС пациентами, получающими иАПФ требуется мониторинг показателей функции почек.

Ключевые слова: *артериальная гипертензия, фармакотерапия, лекарственные взаимодействия, почечная недостаточность, пожилой возраст.*

Түйіндеме

ЕРЕСЕК ЖАС ТОБЫНДАҒЫ ТҮЛҒАЛАРДА БҮЙРЕК ЖЕТІСПЕУШІЛІГІ ДАМУ ҚАУПІНІҢ ФАКТОРЫ РЕТІНДЕГІ БІРІКТІРІЛГЕН ФАРМАКОТЕРАПИЯ

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Кіріспе: Дәрі-дәрмек комбинацияларының (ДЗ) қауіпсіздігі мәселелері дәрігерлердің үнемі назарында, егде жастағы пациенттер ерекше назар аударуды талап етеді. Бұл мәселе әсіресе соңғы жылдары бірнеше ауруларды емдеу үшін дәрілік ем алатын коморбидті пациенттердің полипрагмазия деңгейінің жоғарылауына байланысты өзекті болып отыр. ДЗ өзара әрекеттесу механизмдерін білгендіктен дәрі-дәрмектердің комбинациясының жағымсыз әсерінің салдарын болжауға және алдын алуға болады.

Мақсаты: егде жастағы адамдарда гипертензияға қарсы және антиагрегантты препараттарды бірге қолданған кезде АГ фармакотерапиясының асқынуының қауіп факторларын анықтау.

Материалдар және әдістер: Зерттеу дизайны-бір орталықты рандомизацияланған болашағы бар клиникалық зерттеу. Зерттеуге амбулаториялық және стационар жағдайында 3 жылдан астам (орташа бақылау мерзімі 4,1±1,0 жыл) бақыланған 343 пациент енгізілді. Оның ішінде әйелдер 209, ерлер 134 болды. 66-70 жас тобында 236 пациент (68,8%), 70 жастан асқан (зерттеу басталған кезде 80 жасқа дейін) – 107 (31,2%) болды. Негізгі нәтижелерді анықтау үшін 2 топқа бөлінген нәтижелерді салыстыру жүргізілді – қан тамырлары және бүйрек асқынулары. Зерттеудің соңғы нүктелері: II дәрежелі бүйрек жеткіліксіздігінің дамуы, науқастың кез келген себеппен қайтыс болуы; коронарлық немесе церебралды қан айналымының жедел бұзылуының дамуы.

Зерттеу нәтижелері: орташа есеппен 4,1±1,0 жыл ішінде алынған деректерді талдау барысында II дәрежелі СБЖ дамуының 104 жағдайы анықталды. Антиагрегантты препаратпен біріктірілген ААФИ қабылдау II дәрежелі СБЖ даму жиілігінің статистикалық маңызды жоғарылауы болды (1,12-ден 1,53-ке дейінгі 95% ДИ кезінде 1,31 жиілік қатынасы).

Қорытындылар: Сонымен, жүрек-қан тамырлары аурулары бар пациенттердің үлкен популяциясы үшін ААФИ пен ҚҚБС препараттарының комбинацияларын қолдану бүйрек жеткіліксіздігінің даму қаупін айтарлықтай арттырады. Мұндай комбинацияны қолданудың ерекше сақтығы мына тәуекел топтарында қажет: егде жастағы пациенттерде, ілеспе БСА және қатар жүретін жағдайларда. ААФИ (ИАПФ) қабылдайтын пациенттер ҚҚБС препараттарын қолданған жағдайда бүйрек функциясының көрсеткіштерін мониторингін жүргізу талап етіледі.

Түйінді сөздер: *артериялық гипертензия, фармакотерапия, дәрілік өзара әрекеттесу, бүйрек жеткіліксіздігі, егде жас.*

Bibliographic citation:

Mussina A.Ye., Tuleutayeva R.Ye., Zhumatay A.B., Kakytayeva A.Ye., Imatullina Zh.B., Zhanekenov A.B., Rakhimzhanova A.A. Combination pharmacotherapy as a risk factor for the incidence of renal failure in the elderly // *Nauka i Zdravookhranenie* [Science & Healthcare]. 2023, (Vol.25) 3, pp. 108-112. *doi 10.34689/SH.2023.25.3.014*

Мусина А.Е., Тулеутаева Р.Е., Жуматай А.Б., Какытаева А.Е., Иматуллина Ж.Б., Жанекенов А.Б., Рахимжанова А.А. Комбинированная фармакотерапия как фактор риска развития почечной недостаточности у лиц старшей возрастной группы // Наука и Здравоохранение. 2023. 3(Т.25). С. 108-112. *doi 10.34689/SH.2023.25.3.014*

Мусина А.Е., Тулеутаева Р.Е., Жуматай А.Б., Какытаева А.Е., Иматуллина Ж.Б., Жанекенов А.Б., Рахимжанова А.А. Ересек жас тобындағы тұлғаларда бүйрек жетіспеушілігі даму қаупінің факторы ретіндегі біріктірілген фармакотерапия // Ғылым және Денсаулық сақтау. 2023. 3 (Т.25). Б. 108-112. *doi 10.34689/SH.2023.25.3.014*

Introduction

Antihypertensive therapy is one of the most common areas in the pharmacotherapy of socially significant diseases. This is due to the high prevalence of arterial hypertension in the population and its dominant role as a risk factor for disability and mortality [1,2]. Simultaneously with the increase in BP, there is a negative impact on the hemostasis system [3]. The high risk of thrombosis in patients with arterial hypertension determines the need for antiaggregant and sometimes anticoagulant therapy [4,5].

At the same time, it is not always possible to use a single drug in antihypertensive therapy, and their combination with each other and with antiaggregants may be dangerous [6,7].

There are a number of factors that increase the risk of adverse effects when applying combinations of antihypertensive drugs and their combinations with antiaggregant drugs. First of all, it is elderly age and the presence of concomitant diseases of internal organs [8,9]. Metabolism of most drugs in the liver and excretion of them or their metabolites through the kidneys determine the main target organs [10]. At the same time, kidney damage itself can worsen the degree of AH [11].

Aim of research: to determine the risk factors of complications of AH pharmacotherapy in the combined use of antihypertensive and antiaggregant drugs in the elderly.

Materials and methods: Study design – A single-center randomized prospective clinical trial.

Inclusion Criteria:

- Age over 65 years;
- presence of arterial hypertension stage II-III;
- Availability of reliable data on patients' use of and adherence to antihypertensives and acetylsalicylic acid as an antiaggregant medication;
- availability of examination results in accordance with the study protocol.

Exclusion criteria:

- symptomatic arterial hypertension;
- The presence of pathology that excludes dynamic analysis of renal function (glomerulonephritis, other renal damages with chronic insufficiency II degree on the moment of examination);
- presence of pathology that is a contraindication to the use of antiaggregant drugs (peptic ulcer and other.).
- declining to participate in the study.

A total of 343 patients followed up on an outpatient and inpatient care basis for more than 3 years (mean follow-up 4.1±1.0 years) were included in the study.

Among them, there were 209 women (60.9%) and 134 men (39.1%). In the age group of 66-70 years there were 236 patients (68.8%), older than 70 years (up to 80 years at the beginning of the study) - 107 (31.2%). The mean age of the examined patients was 69.7±4.3 years. The history of arterial hypertension ranged from 5 to 20 years or more (mean, 12.7±3.2 years).

All patients had concomitant diseases of the musculoskeletal system, respiratory system, gastrointestinal tract, nervous system and others. The number of comorbidities ranged from 4 to 17 (mean 7.2±1.3).

The methods of examination of patients included a complex corresponding to the Protocols of Diagnosis and Treatment of Arterial Hypertension.

To determine the achievement of the target BP and the degree of deviations from it, daily monitoring of the BP profile with calculation of the main parameters was performed once every 6 months.

In addition, methods of renal function testing (creatinine determination, GFR) were used in the framework of the work, applied once every 6 months or, in the presence of deterioration detected in the previous period - once every 3 months. In the presence of further deterioration in the dynamics, the attending physicians were given recommendations to change antihypertensive and (or) antiaggregant therapy.

To determine the main results, we compared outcomes classified into 2 groups - vascular and renal complications. The endpoints of the study were: development of renal failure II stage, patient death from any cause; development of acute coronary or cerebral circulatory failure.

Results of investigation

Figure 1 shows the distribution of drug groups and their combinations that were used in the treatment of arterial hypertension in the study population.

In the treatment of AH in older patients, a wide range of drugs was used, both those obtained from the health insurance system and those purchased by patients. As a result, the structure was diverse and there was no significant dominance of any class or combination. The most commonly used combinations and/or combination medications included an ACE inhibitor and a diuretic, as well as a calcium antagonist and an ACE inhibitor and a calcium antagonist and a diuretic. The remaining treatment options accounted for 42.3%.

Acetylsalicylic acid in dosage ranging from 0.25 g to 0.375 g was used as an antiaggregant drug in all cases.

According to the literature, the combination of ACE inhibitors and aspirin has been identified as the most dangerous for renal function [12,13].

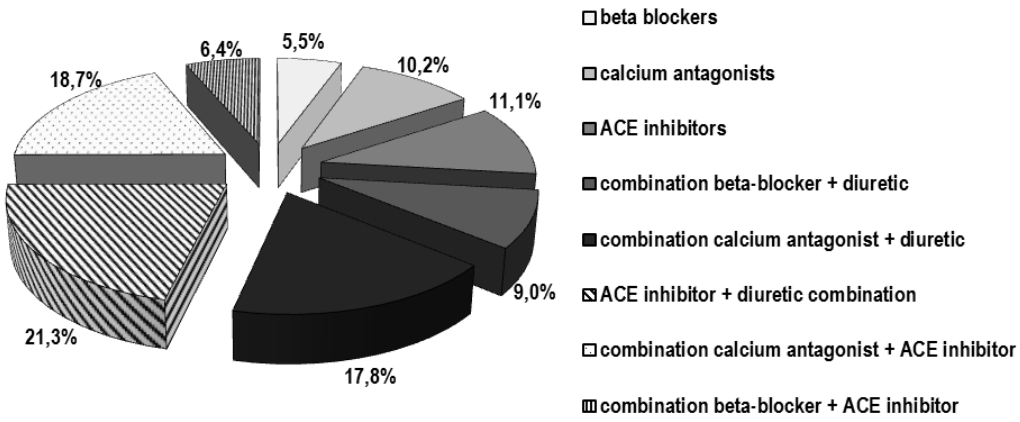

Figure 1. Structure of drugs, their combinations and combined drugs (included in combinations) used in the treatment of the examined patients

There were three main components to analyzing the results of the study:

- reaching the "end point" - development of II stage CRF, stroke, MI.
- defining the level of BP by daily monitoring;
- defining the dynamics of renal function by analyzing laboratory parameters. The incidence rates of the endpoints are presented in Fig 2.

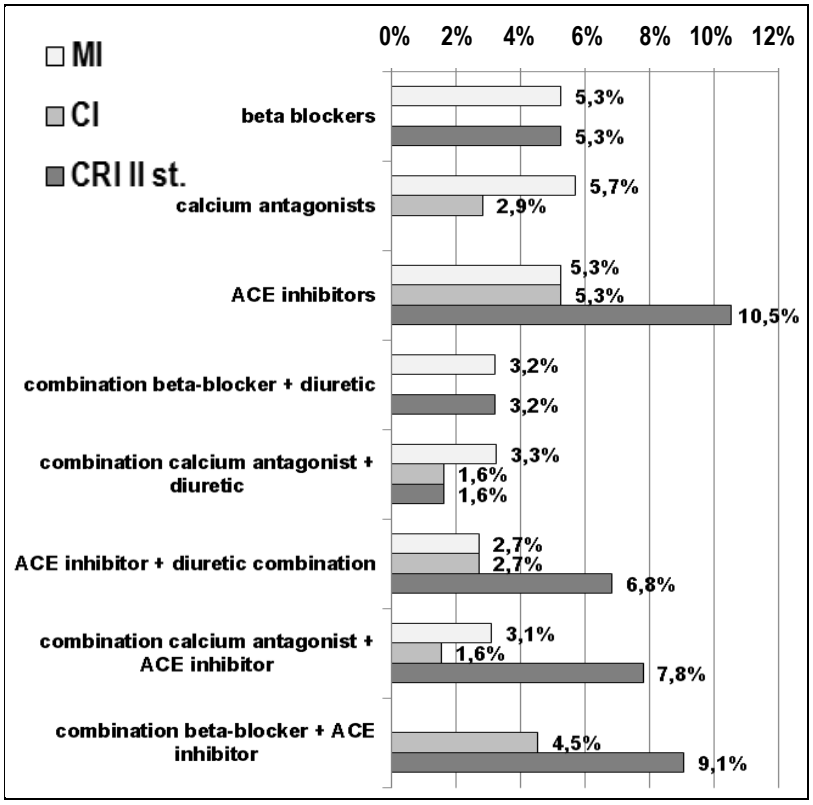

Figure 2. The incidence rates of the endpoints

The overall incidence of study endpoints was significantly higher in the ACE inhibitor use group.

This conclusion was made only due to the frequency of cases of CRF II stage and higher. Differences on this parameter were also significant ($\chi 2=5.899$ $p=0.016$).

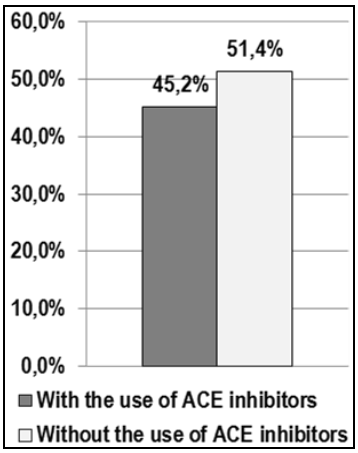

Figure 3. Frequency of achievement of target BP in the examined patients depending on the use of ACE inhibitors, including in combinations.

Discussion

During the analysis of data obtained during average 4.1±1.0 years, 104 cases of CRF II stage development were identified. Combined use of ACE inhibitors with antiaggregant drug was accompanied by statistically significant increase in the incidence of CRF II stage. (frequency ratio 1.31 with 95% CI 1.12 to 1.53). Co-administration of antihypertensive and anti-inflammatory drugs is accompanied by an increased risk of CRF development.

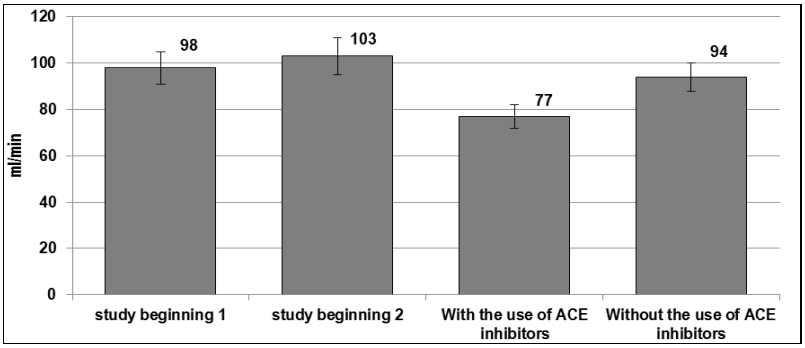

Figure 4. Creatinine concentration according to treatment in patients at the beginning and at the end of the study.

The highest risk of CRF development is observed in the group of patients taking antihypertensive therapy with ACE inhibitor in combination with acetylsalicylic acid. Despite the positive effect of taking antihypertensive drugs on the risk of cardiovascular complications, it is necessary to be careful when combining them with NSAIDs. The use of NSAIDs increases the risk of kidney damage in patients with concomitant cardiovascular disease who take diuretics and ACE inhibitor. The combination of ACE inhibitor +diuretics and NSAIDs may be associated with renal dysfunction due to the interaction of pharmacodynamic effects on renal hemodynamics, vascular tone and volemia [14, 15].

Conclusion

When NSAIDs combined with an ACE inhibitor, which have a nephroprotective effect, there is an antagonistic effect of NSAIDs on the kidneys. However, the triple combination of NSAIDs+ACE inhibitor+diuretics leads to severe impairment of renal function - iatrogenic nephropathy, which can be fatal [16,17]. This combination has been named "triple whammy" - "dangerous TRIO", recognized by the World Health Organization as a dangerous combination requiring special monitoring of renal function and the need to avoid use in clinical practice especially at elderly patients. [18,19].

Authors' contributions. *Author contribution statement: All authors were equally involved*

Conflict of Interest. *The authors declare that they have no competing interests.*

Funding Source. *The research was funded by the Semey Medical University as part of a doctoral dissertation.*

Acknowledgements. *We gratefully acknowledge assistance and support of the management of the NAO "Semey Medical University", Semey, Kazakhstan. We also want to express our gratitude to all patients who participated in the study.*

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