



# Effect of omeprazole on antihypertensive efficacy of amlodipine in patients with comorbid pathology – arterial hypertension and acid-dependent disease

Margarita N. Dorofeeva<sup>1</sup>, Evgeniya V. Shikh<sup>1</sup>, Zhanna M. Sizova<sup>1</sup>, Natalya N. Shindryaeva<sup>1</sup>, Natalya I. Lapidus<sup>1</sup>

## ABSTRACT

**Objective:** The problem of drug interactions is increasingly important today because they may induce serious adverse events as well as interfere with efficacy of pharmacotherapy. Combinations of drugs are most often prescribed to patients presenting with comorbid pathology. The incidence of a combination of arterial hypertension (AH) and acid-dependent diseases (ADDs) varies widely ranging from 11.6 to 50%. One of combinations of drugs prescribed to such patients is a combination of calcium channel blocker amlodipine and proton pump inhibitor omeprazole. The latter in the human body undergoes biotransformation mediated at the level of cytochrome P450 by isoenzymes CYP2C19 and CYP3A4. Amlodipine is a substrate of the isoenzyme CYP3A4, which increases the probability of the development of interaction between these drugs. The purpose of our study was to investigate antihypertensive efficacy of amlodipine in patients suffering from arterial hypertension combined with acid-dependent diseases and additionally taking omeprazole.

**Method:** Study included a total of 150 patients with AH and ADD. Antihypertensive therapy was evaluated by means of office measuring of arterial pressure (AP) and circadian monitoring of AP (CMAP). The followed-up patients with AH and ADD were divided into 2 groups. Group One was composed of hypertensive patients undergoing pharmacotherapy with 10 mg amlodipine, whose condition required due to exacerbation of ADD administration of omeprazole at a dose of 20 mg for a period from 3 to 4 weeks. Group Two comprised hypertensive patients receiving antihypertensive therapy consisting of 10 mg amlodipine, who were found to have remission of acid-dependent diseases, with no additional medication taken.

**Results:** The obtained findings demonstrated that one of the commonly used drug combinations in treatment of patients with AH and ADD in ambulatory conditions was a combination of omeprazole and amlodipine, accounting for 7.1%. The results of office measurement of arterial pressure (AP) 2 weeks after initiating pharmacotherapy with omeprazole in patients with AH and ADD demonstrated that the patients receiving omeprazole in addition to antihypertensive therapy were found to have a statistically significant decrease in systolic arterial pressure (SAP) and statistically significantly more pronounced dynamics of a decrease in diastolic arterial pressure (DAP) ( $p < 0.05$ ) compared with those not receiving therapy with omeprazole. Also, in the group of patients taking omeprazole, the findings of circadian monitoring of blood pressure (CMAP) showed a statistically significant decrease in average circadian SAP, average circadian DAP, mean value of daytime SAP and mean value of nighttime SAP ( $p < 0.05$ ).

**Conclusion:** The obtained findings demonstrated that simultaneous prescription of amlodipine and omeprazole to patients with concomitant pathology, i.e., AH and ADD, turned out to enhance the antihypertensive affect of amlodipine, which probably resulted from substrate competition of amlodipine and omeprazole at the level isoenzyme CYP 3A4 of cytochrome P450.

**Keywords:** omeprazole, amlodipine, isoenzyme CYP 3A4, arterial hypertension, acid-dependent diseases

## INTRODUCTION

Drug interaction is currently an increasingly important problem of modern pharmacotherapy since it may considerably alter the pharmacodynamic activity of drugs and be a cause of failed therapy or a decrease of its safety (1-4).

Widely used for treatment of acid-dependent diseases, omeprazole in the human body undergoes rapid and intensive biotransformation mediated by isoenzymes CYP2C19 and CYP3A4, thus increasing the probability of the development of drug interaction with other substrates or inhibitors of these enzymes (5, 6). The question arises of whether this alteration in the activity of isoenzyme CYP3A4 can lead to clinically significant interactions (altered activity) of drugs metabolised

<sup>1</sup> Chair of medical and social assessment, urgent and ambulatory care. First Moscow State Medical University named after I. M. Sechenov, Moscow, Russia

**Correspondence:** Margarita N. Dorofeeva  
Chair of, of medical and social assessment, urgent and ambulatory care  
First Moscow State Medical University named after I. M. Sechenov, Moscow, Russia

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E-mail: [margaritadorofeeva@yandex.com](mailto:margaritadorofeeva@yandex.com)

**Table 1:** Clinical characteristics of patients with AH and ADD enrolled into the study

Parameters		Number of patients	
		n	
		Group Two amlodipine n = 99	Group One amlodipine + omeprazole n = 51
Gender	Male	45 (45.45%)	24 (47.05%)
	Female	54 (54.54%)	27 (52.94%)
Mean age, years		54.6 ± 5.6	
Duration of AH, years	up to 5 years	49 (49.49%)	28 (54.9%)
	from 5 to 10 years	28 (28.28%)	14 (27.45%)
	More than 10 years	22 (22.2%)	9 (17.64%)
AH Stages	Stage I	20 (20.20%)	10 (19.6%)
	Stage II	51 (51.51%)	33 (64.7%)
	Stage III	28 (28.30%)	8 (15.7%)
AH Degree	Degree 1	19 (19.19%)	9 (17.64%)
	Degree 2	60 (60.60%)	35 (68.62%)
	Degree 3	20 (20.20%)	7 (13.72%)
ADD	Gastritis	59 (59.6%)	22 (22.2%)
	GERD	23 (23.23%)	18 (35.29%)
	PUD, in remission	17 (17.17%)	11 (21.56%)

via this enzyme and influence the clinical efficacy of drugs (7,8). Taking into consideration frequent administration of omeprazole in patients with ADD and AH in ambulatory practice, this problem requires further study.

## MATERIALS AND METHODS

At the first stage of the study we analysed a total of 1,126 out-patient medical case histories in order to reveal the incidence rate of the combination of AH and ADD in the setting of a municipal polyclinic.

At the second stage of the study we analysed pharmacotherapy of patients with accompanying pathology – ADD (analysis of the most commonly prescribed combinations of drugs, drug interactions with regard for metabolism, as well as assessment of the risk for the development of adverse drug reactions (ADRs) at the level of cytochrome P450 CYP3A4 with the help the Internet-resource drugs.com).

At the third stage, the study included a total of 150 patients with AH and ADD, aged above 18 years, followed up in the ambulatory-polyclinic link and having signed informed consent for participating in the study. The exclusion criteria were as follows: a history of endured acute impairment of cerebral circulation and transitory ischaemic attack, myocardial infarction during the previous year, severe cardiac arrhythmia and impaired conductivity, chronic heart failure, chronic liver diseases, chronic kidney disease, adrenal diseases, and patients taking glucocorticoids.

To be included into the study, all patients underwent a standard procedure: taking case history, anthropometric measurements (height, weight), physical examination, instrumental and laboratory examination.

Antihypertensive therapy was evaluated by means of two methods: office measuring of AP and circadian monitoring of AP (CMAP). Office measurement of AP was carried out at each visit, CMAP was conducted two times: before starting to take a combination of amlodipine with omeprazole and at 2 weeks of combined pharmacotherapy.

Office measurement of AP was performed in a seated position after a 15-minute rest period by the Korotkov technique, measuring AP twice with a 3-minute interval, followed by calculation of the mean value. Circadian monitoring was carried out during 24 hours by means of the Russian-made software-hardware complex "BPLab".

The followed-up patients with AH and ADD were divided into 2 groups. Group One was composed of hypertensive patients undergoing pharmacotherapy with 10 mg amlodipine, whose condition required due to exacerbation of ADD administration of omeprazole at a dose of 20 mg for a period from 3 to 4 weeks.

Group Two comprised hypertensive patients receiving antihypertensive therapy consisting of 10 mg amlodipine, who were found to have remission of acid-dependent diseases, with no additional medication taken (**Table 1**).

## RESULTS

The analysis of 1,126 ambulatory medical case histories of patients with AH followed up at the Municipal Polyclinic № 2 of the Moscow Healthcare Department showed that 150 (13%) patients with AH were diagnosed with ADD. This

cohort was represented predominantly by 30-to-67-year-old patients with chronic gastritis (58%). The clinical characteristics of these patients are shown in **Table 1**.

Analysing the names and frequency of prescribing antihypertensive drugs demonstrated that most frequently prescribed were the following ACE inhibitors: perindopril – 23 (4.4%) patients, enalapril – 30 (6.2%), lisinopril – 17 (3.5%), fosinopril – 7 (1.5%), berlipril – 2 (0.4%), quinapril – 1 (0.2%) patient. As angiotensin II receptor antagonist (ARA II) the following drugs were used: valsartan in 21 (4.4%) patients, losartan in 32 (6.6%) patients, olmesartan in 11 (2.3%) patients and azilsartan in 8 (1.7%). Amongst beta-adrenoblockers (BABs) most often used were the following drugs: bisoprolol in 41 (8.5%) patients, metoprolol – 25 (5.3%) subjects, atenolol in 5 (1.1%) patients, carvedilol in 3 (0.6%) patients, and betaxolol in 13 (2.7%) patients. Of the calcium channel blockers, amlodipine was taken by 42 (8.7%) patients, felodipine by 19 (3.9%) patients, lercanidipine by 8 (1.7%). Of diuretics, mention should be made of indapamide – 9 (1.9%) patients, and hydrochlorothiazide – 18 (3.7%) patients.

Hence, the most often used drugs possessing antihypertensive activity in patients with AH and ADD in ambulatory practice were bisoprolol taken by 8.5% and amlodipine taken by 8.7%.

Analysing the names and frequency of prescribing antisecretory drugs demonstrated that patients with concomitant pathology, i.e. AH and ADD, most often received proton pump inhibitors: omeprazole – 92 (19.1%) patients, pantoprazole – 27 (5.6%), and esomeprazole – 19 (3.9%) patients. Of another group of agents decreasing secretion of hydrochloric acid mention should be made of histamine H<sub>2</sub>-receptor blockers such as ranitidine – 3 (0.6%) cases and famotidine – 9 (1.9%) cases.

Analysing combined pharmacotherapy in 150 patients with AH and ADD demonstrated that amongst a total of 92 cases of omeprazole with ACE inhibitors, most often encountered were combinations with enalapril – 18 (3.9%) patients, perindopril – 11 (2.4%) patients, lisinopril – 7 (1.5%) patients and fosinopril – 7 (1.5%) patients.

Amongst combinations of omeprazole with ARAs II most often encountered was omeprazole combined with valsartan – 20 (4.3%) patients. Omeprazole combined with losartan was prescribed to 8 (1.7%) patients and with olmesartan to 5 (1.1%) patients.

Amongst combinations of omeprazole with BABs, most frequently encountered was a combination with bisoprolol – 28 (6.1%) patients, metoprolol – 19 (4.1%). A combination of omeprazole and carvedilol was prescribed in 0.6% of cases.

Of the combinations of omeprazole with calcium channel blockers, most often encountered was a combination with amlodipine – 33 (7.1%) cases. Simultaneous administration of omeprazole and felodipine accounted for 1.9% (9 patients).

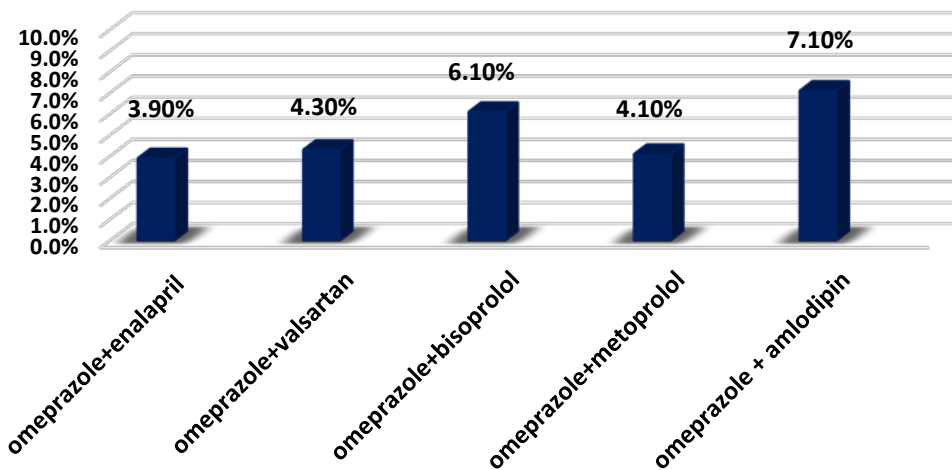
Pantoprazole was prescribed in the composition of 19 various combinations with antihypertensive drugs, amongst which mention can be made of the most frequently used in out-patient practice combinations: with enalapril – 6 (1.3%) patients, valsartan – 4 (0.9%), losartan – 6 (1.3%), and bisoprolol – 6 (1.3%) patients.

Esomeprazole was prescribed in the composition of 12 various combinations with antihypertensive drugs: most often with perindopril – 6 (1.3%) patients, valsartan – 3 (0.6%), amlodipine – 4 (0.9%), metoprolol – 5 (1.1%), bisoprolol – 4 (0.9%) patients (**Table 1**).

Hence, the most commonly used in out-patient practice combinations in treatment of patients with AH and ADD were as follows: omeprazole with enalapril – 18 (3.9%) patients, with valsartan – 20 (4.3%), with bisoprolol – 28 (6.1%), with metoprolol – 19 (4.1%). The most frequently used combination in treatment of patients with AH and ADD according to the findings of the analysis of medical case histories was a combination of omeprazole and amlodipine: 33 (7.1%) patients (**Figure 1**).

We examined the dynamics of AP in patients with AH and ADD, being on adjusted antihypertensive therapy consisting of amlodipine at a dose of 10 mg, who due to exacerbation of ADD were additionally prescribed omeprazole at a dose of 20 mg.

The results of office measurement of AP 2 weeks after the beginning of pharmacotherapy with omeprazole in patients with AH and ADD demonstrated that the patients receiving antihypertensive therapy with amlodipine supplemented by omeprazole due to exacerbation of ADD were found to have a statistically significant decrease in SAP, statistically significantly more pronounced dynamics of a decrease in DAP ( $p < 0.05$ ) as compared with the group of patients not receiving therapy with omeprazole.



**Figure 1:** Most frequently prescribed in out-patient practice combinations of drugs with antihypertensive and antisecretory activity

**Table 2:** Dynamics of AP in patients on the background of pharmacotherapy

24-hour monitoring of AP			
<b>Mean circadian SAP, mm Hg</b>	137.3 ± 4.8	135.7 ± 3.9	
	132.5 ± 5.5	123.5 ± 4.3	0.04
Dynamics of mean office SAP	5.1 ± 1.5	12.7 ± 2.7	0.04
Dynamics of mean office SAP in Δ%	3.7 ± 0.8	10.3 ± 3.4	0.04
<b>In-group p</b>	0.04	0.03	
<b>Mean DAP circ., mm Hg</b>	86.7 ± 3.4	86.7 ± 3.1	
	82.4 ± 3.4	75.5 ± 3.9	0.06
Dynamics of average circadian DAP	4.7 ± 1.7	11.2 ± 2.9	0.04
Dynamics of average circadian DAP in Δ%	4.9 ± 1.6	12.91 ± 3.5	0.04
<b>In-group p</b>	0.04	0.04	
<b>Mean daytime SAP, mm Hg</b>	137.6 ± 4.6	136.9 ± 4.4	
	135.9 ± 5.1	122.6 ± 5.7	0.04
Dynamics of mean daytime SAP, mm Hg	1.7 ± 0.7	14.3 ± 2.6	0.04
Dynamics of mean daytime SAP, mm Hg Δ%	1.23 ± 2.2	10.4 ± 2.8	0.04
<b>In-group p</b>	0.04	0.04	
<b>Mean nighttime SAP, mm Hg</b>	131.2 ± 4.3	130.5 ± 4.27	
	128.5 ± 5.2	120.4 ± 4.8	0.04
Dynamics of mean nighttime SAP, mm Hg	3.61 ± 1.1	9.9 ± 1.8	0.04
Dynamics of mean nighttime SAP, mm Hg Δ%	2.75 ± 1.3	7.5 ± 2.1	0.04
<b>In-group p</b>	0.04	0.04	
<b>Mean daytime DAP, mm Hg</b>	87.3 ± 3.5	87.5 ± 3.7	
	83.6 ± 5.7	80.7 ± 5.6	0.06
Dynamics of mean daytime DAP, mm Hg	4.38 ± 1.3	6.8 ± 2.2	0.06
Dynamics of mean daytime DAP, mm Hg Δ%	5.2 ± 1.8	7.9 ± 2.1	0.06
<b>In-group p</b>	0.04	0.02	
<b>Mean nighttime DAP, mm Hg</b>	85.8 ± 6.1	85.7 ± 6.2	
	76.8 ± 5.9	74.5 ± 6.3	0.05
Dynamics of mean nighttime DAP, mm Hg	9.2 ± 2.1	11.2 ± 2.3	0.05
Dynamics of mean nighttime DAP, mm Hg Δ%	10.48 ± 3.4	13.06 ± 2.7	0.05

The results of CMAP 2 weeks after the beginning of pharmacotherapy with omeprazole in patients with AH and ADD demonstrated that the patients additionally to therapy taking omeprazole had a statistically significant decrease in average circadian SAP, average circadian DAP, average value of daytime SAP, mean value of nighttime SAP ( $p < 0.05$ ) as compared with the group of patients not receiving therapy with omeprazole. The patients undergoing therapy supplemented with omeprazole were also found to have a slightly more pronounced decrease in mean daytime DAP and nighttime DAP, which, however, was not statistically significant ( $p > 0.05$ ) (Table 2).

## DISCUSSION AND CONCLUSIONS

The findings of analyzing the primary medical records of patients demonstrated that the frequency of combination of AH and ADD in out-patient clinical practice amounted to 13%.

The incidence and probability of concomitant lesions of the digestive and cardiovascular systems are determined by the commonness of many factors responsible for the development of both gastroenterological and cardiovascular diseases, in particular, an increase in the aggregation properties of erythrocytes and blood platelets, systemic impairments at the level of arterioles, hypertrophy of smooth-muscle cells of vessels, impaired endothelium-derived vasodilators, neuroendocrine alterations (9,10).

The presence and progression of inflammatory alterations of the oesophageal and duodenal mucous membranes in the patient cohort concerned appear to contribute to formation of a particular AP profile (11). Close pathogenetic interrelations in the form of systemic impairments at the level of arterioles, neuroendocrine shifts, and changes in haemostasis have been confirmed (12). Studies of other authors demonstrated that haemodynamic disorders characteristic of AH play a significant role in the pathogenesis of acid-dependent diseases (13-15).

A comorbid condition of patients, as a rule, requires prescription of several drugs. The findings of our study showed that the most frequently prescribed combination of drugs in patients with AH and ADD was that of omeprazole and amlodipine.

The key reaction of phase I metabolism of omeprazole is formation of 5-hydroxiomeprazole, catalyzed by CYP2D19 and CYP3A4. Affinity of omeprazole to 3A4 is 10 times lower than that to 2C19, therefore, metabolism via 3A4 is considered as an alternative pathway while creating high concentrations of omeprazole in blood plasma of patients (16-19).

The known fact is that most drugs used for treatment of cardiovascular diseases are metabolized by isoenzyme of cytochrome P450 3A4, including also amlodipine (20). In this connection, we studied possible influence of omeprazole on antihypertensive efficacy of amlodipine in patients with AH and ADD.

Characteristic of amlodipine is a direct correlation between the degree of the antihypertensive effect and plasma concentration. One of the factors determining the concentration of the drug is metabolism intensity which, in turn, depends on the activity of amlodipine-metabolizing isoenzyme cytochrome CYP3A4 (21, 22).

Omeprazole has a dual-pathway metabolism: via CYP 2C19 and CYP 3A4. In case of the presence of a particular genetic polymorphism of isoenzyme of cytochrome CYP 2C19 P450, metabolism of omeprazole may be shifted towards CYP 3A4 P450, which, probably, may lead to a decrease in the activity of CYP 3A4, slowing-down of amlodipine metabolism and, as a consequence, to an increase in its concentration in blood plasma (23-25). Elevated blood plasma amlodipine leads to enhancement of the antihypertensive effect, which we observed in patients who on the background of antihypertensive therapy with amlodipine were taking pharmacotherapy with omeprazole due to exacerbation of acid-dependent diseases. Patients undergoing therapy with amlodipine supplemented with omeprazole were found to have a statistically significant decrease in average circadian SAP, average circadian DAP, mean value of daytime SAP, mean values of nighttime SAP ( $p < 0.04$ ) as compared with patients not taking therapy with omeprazole.

Simultaneous administration of amlodipine and omeprazole in patients with AH and ADD turned out to enhance the antihypertensive effect of amlodipine, which probably is the result of substrate competition of amlodipine and omeprazole at the level of isoenzyme of cytochrome CYP 3A4 P450.

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