Original article

Pharmacokinetics of Angiotensin-Converting Enzyme Inhibitors in Elderly Patients with Arterial Hypertension

Elizaveta Mikhailova[1], Natalya Chernus[2], Elena Egorova[3], Roberto Lozano[4]

Abstract

Objective: With the gradual aging of the world's population, selecting an effective treatment regime for arterial hypertension (AH) becomes increasingly important. This article aims to analyze the pharmacokinetic and pharmacodynamic properties of parent enalapril and generic drugs in elderly patients suffering from AH. ***Materials and methods:*** The study is randomized, implying random distribution of patients into study groups. The study was conducted in 2018 among 200 patients diagnosed with AH. All elderly patients (mean age 77.5 ± 1.5 years) were divided into two equal groups. Group 1 was prescribed 10 mg of original enalapril orally, and Group 2 similarly took 10 mg of generic enalapril. The blood pressure of all patients was measured 1, 2, 4, 6, 8, and 11 hours after dosing and one day after treatment. Also, blood samples were taken after blood pressure measurements. ***Results and Discussion***: After 1 hour, differences between Groups 1 and 2 ($p \leq 0.001$) were found at the level of 29.84 ng/1 ml for the original drug and 19.01 ng/1 ml for the generic. Further, these values were 38.2 ng/1 ml vs. 28.7 ng/1 ml ($p \leq 0.001$) after 2 hours, 36.6 ng/1 ml vs. 26.5 ng/1 ml ($p \leq 0.001$) after 4 hours, and 9.2 ng/1 ml vs 5.1 ng/1 ml ($p \leq 0.001$) after 24 hours, respectively. The maximum concentration-time curve values for both medications corresponded to the period of 2 hours after administration. ***Conclusion:***Thus, generics are much less effective as an antihypotensive medication than the original enalapril.

Keywords: Antihypotensive effect, enalapril original, generic drug, hypertension, senile age.

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Introduction

To date, the targeted reduction of blood pressure parameters prevails among current approaches for secondary prevention of AH [1]. Furthermore, the therapy aims to reduce death rates, mainly due to the failures in such vital organs as the heart, brain, and kidneys. Findings of some clinical trials suggest that a combination of 2 or more drugs is more effective for patients diagnosed with AH [2]. Therefore, combined therapy in hypertensive patients is the primary approach with acceptable outcomes (lower blood pressure, lower mortality) [3]. Regarding the risk of complications and even cardiovascular accidents in patients diagnosed with AH II, III, and sometimes I degrees, combination therapy is recommended, without an intermediate stage of treatment with a single drug (monotherapy) [4]. The simplification of this approach is also determined by the drug specificity. For example, the two drugs can be contained in one pill [5].

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The effectiveness of various antihypertensive drug combinations in the treatment of AH is intensively investigated [6]. In most cases, two treatment regimesare applied. The first involves the combination of an angiotensin-converting enzyme (ACE) inhibitor and a thiazide diuretic, recognized in Western practice [7,8]. The principal positive effect of this combination is obtained by reducing the synthesis of angiotensin 2. According to some studies, the maximum effect of this combination was observed in patients with a high activity of the renin-angiotensin-aldosterone system [9]. However, diuretic therapy has certain limitations since patients may develop pathological conditions, such as reactive hyperreninemia and hyperaldosteronemia, which are also associated with the activity of the renin-angiotensin-aldosterone system. These syndromes are relieved by a combination of diuretics and ACE inhibitors. Another advantage of the therapy using two medications is a fairly rapid return of blood pressure to average values, corresponding to the target values. Angiotensin inhibitors demonstrated rather low efficacy in patients with low and normal renin system activity [10]. At the same time, when these medications are combined, the activity of the renin system and the sensitivity of angiotensin inhibitor receptors increase. Consequently, this therapy is harmless for patients with different forms of AH [11]. Using an ACE inhibitor prevents the onset of hypokalemia due to reduced aldosterone and angiotensin 2 levels. Hence, potassium can be absorbed backward, even if diuretics are prescribed. At the same time, the excretion of sodium from the body can be observed [12]. Adverse effects of diuretic treatment include, among others, changes in metabolic levels (carbohydrates, lipids, purines). In contrast, the concentration of such compounds as uric acid, glucose, and cholesterol increases [13]. These negative effects are mitigated by combining diuretics and ACE inhibitors. Negative effects of combined therapy include the high probability of developing hypotension during the first administration and a decrease in renal function, especially together with heart failure. Consequently, in combination treatment, the dose of both drugs shall be gradually reduced, allowing for an antihypertensive effect to be achieved. At the same time, the probability of adverse events is very low [14]. According to clinical trials, a diuretic and ACE inhibitor combination allows most patients (80%) to achieve the target blood pressure level [15]. This therapy is also recommended for elderly and senile patients if they suffer from isolated systolic arterial hypertension or monotherapy with diuretics and ACE inhibitors did not show the desired results. Because of the undesirable effects on the metabolism of carbohydrates and lipids, diuretics, especially thiazide, are prescribed at low doses.

When choosing a specific drug among ACE inhibitors, the pharmacokinetic characteristics of that drug are usually taken into account, namely, its availability and transformation in the body and possible routes of elimination and reduction of angiotensin activity [16]. Naturally, long-acting (one day) ACE inhibitors are the most preferred. However, if the pathway of this drug excretion is through the kidneys, the drug dose should be chosen concerning renal insufficiency. Additionally, the effect of ACE inhibitors will also be reduced in the case of various functional liver disorders) [17]. Therefore, ACE inhibitor drugs are divided into the following groups according to their pharmacokinetic properties [15]: a) active drugs (Captopril and Lisinopril); b) prodrugs, which are precursors of inhibitors. They include Fosinopril and the whole class of carboxyalkyl dipeptides, except for Lisinopril in the first group. Prodrugs are characterized by a transition to the active form when ingested by the gastrointestinal tract but are ineffective against liver failure. In general, for medicinal products in this group, a longer effect is observed relative to the first group. This combination is, therefore, indicated for elderly and senile patients.

According to the results of ASCOT [18], another combination of ACE inhibitors (with calcium antagonists) is receiving considerable attention in the treatment of arterial hypertension. Both types of drugs have a similar effect of reducing blood pressure levels due to their involvement in vasodilation. Sodium excretion is also typical of these drug classes. At the same time, the two classes of drugs are different in how they contribute to achieving the desired effect. Whereas the ACE inhibitor achieves its effect due to the renin system, the calcium antagonist is characterized by blocking the possibility of Ca_2 ions entry into the cell. Hence, the maximum effect of these drugs is possible when used in combination for patients with high and low renin system activity in AH. Both drugs complement each other also because they relieve or strongly revert side effects. Thus, dry cough occurring when using an ACE inhibitor is reduced when combined with a calcium antagonist, and the progression of peripheral edema, typical of antagonist use, is reduced by using an ACE inhibitor. Both drugs have organ protective effects,

particularly on the kidneys. The condition of the kidneys in AH patients is known to be significantly aggravated by the high pressure within the renal glomerules. Both drugs positively affect afferent and efferent glomerular vessels when used together. Hence, the target values of diastolic blood pressure were reached nearly in all patients (90%) due to the combined intake of Felodipine and ACE inhibitor.

Elderly patients constitute a significant share of the population in many countries worldwide. Some projections suggest that by 2025, a seventh (1 billion) of the human population will be over the age of 60 [11]. At that, AH predominates among the most common diseases of elderly and senile patients [10]. Therefore, effective treatment of this disease requires proper tactics of hypotensive drugs selection to be applied, which specifies the relevance of the present study. Existing literature suggests that there is no identity in the determination of pharmacodynamic and pharmacokinetic parameters of antihypotensive drugs for the elderly and the elderly [11]. The authors of the present study attempted to accomplish this. It is assumed that the pharmacokinetics of the original and generic enalapril drugs studied will differ in older people due to the particularities of body metabolism.

The study's objective was to examine the pharmacokinetics and pharmacodynamics of using original and generic enalapril in older patients diagnosed with AH. The authors have set the following tasks: a) to analyze the pharmacokinetic properties of enalapril in elderly patients; b) to identify the possible relationship between pharmacokinetic and pharmacodynamic properties of the drug during therapy.

Materials and Method

Sampling

The study was conducted in January-December 2018 in one of the cardiology centers in Moscow (Russian Federation). The study was randomized. Patients were randomly assigned to particular groups using closed envelopes. The study involved patients aged over 75 years, i.e., according to the age criteria corresponding to senile age. The sample consisted of 200 patients with a history of AH. The mean age of the patients was 77.5 ± 1.5 years. Of all patients, 86 were males (mean age 79.4 ± 3.6 years), and 114 were females (mean age 77.1 ± 1.0 years). Detailed information on the sample is presented in Table 1. Gender differences were not considered in the present study, as the average age of men and women was comparable. All patients were randomly assigned to two groups of 100 patients each. Bodyweight and type of AH, i.e., systolic-diastolic or isolated systolic hypertension, were also considered when dividing patients into groups. Group 1 included patients prescribed with the original Enalapril drug by Renitec (with active ingredient Enalaprilum, manufactured by Merck Sharp & Dohme Idea Inc., the Netherlands). Patients in Group 2 patients received generic enalaprilEnam, i.e., a drug bioequivalent to the original (Enam, manufactured by Dr. Reddy's Laboratories Ltd., India, with active ingredient enalapril).

Table 1. Key parameters of the studied patients

Parameters	Group 1		Group 2	
	M	F	M	F
Number of patients	35	65	51	49
Age, years	79.2	77.2	79.6	76.9
Weight, kg	82	73	83	75
Systolic-diastolic hypertension, number of patients	25	41	32	28
Isolated systolic hypertension, number of patients	10	24	19	21

Research Protocol

Patients in all groups terminated an ACE inhibitors intake one week before the start of the study. At the beginning of the study, patients in Group 1 took 10 mg of original enalapril, and patients in Group 2 received the same dose of generic enalapril. The drug was administered in the morning. Before each blood sampling period, systolic, diastolic, and pulse blood pressure levels were measured in all patients. In order to examine the pharmacokinetics of the drug, a blood sample was taken from the ulnar vein. The volume of blood sampled amounted to 3 ml. Samples were taken 1, 2, 4, 6, and 8 hours after drug intake, then after 11 and 24 hours. The selected samples were placed in Eppendorf tubes and refrigerated to -20ºC until the time of the study. The pharmacokinetic properties of the original and generic enalapril were studied by chromato-mass spectrometry using Agilent Technologies 1200 (USA). For establishing the nature of pharmacokinetics, the following parameters were considered: (a) values of maximum drug concentration (c), in nanograms of substance per 1 ml of blood plasma, ng/ml; (b) period of reaching maximum drug concentration in blood plasma (tmax), in hours; (c) similarly, a period of drug retention in the blood plasma (tconc), also in hours; (d) values of area under the pharmacokinetic curve (S), in ng h/ml, the period from zero to infinity.

Statistical Analysis

The obtained data were initially entered into Excel 2016 database (Microsoft Corp., USA), and statistical analyses were performed using Statistica v.7.0 software (StatSoft Inc., USA). The arithmetic mean and error of the mean for each of the pharmacokinetic parameters, as well as the upper and lower limits, were calculated. Since the distribution did not follow the normal, the non-parametric analytical methods, such as the chi-square test, the Mann-Whitney test, and the Wilcoxon test, were used. The minimum level of difference significance between the groups was $p \leq 0.05$.

Results

Pharmacokinetics of Original and Generic Enalapril

The following results were determined for the oral administration of the parent enalapril and generic drugs (Table 2).

Table 2. Comparative indicators of pharmacokinetics at a single administration of original and generic enalapril

Parameter and drug name	Maximum drug concentration values, ng/ml	Time of reaching the maximum drug concentration in blood plasma, hours	Area under the pharmacokinetic curve, ng/h/ml	Period of drug retention in blood plasma, hours
The original drug	(28.99-33.01) 31.69	(1.95-2.10) 2.00	(134.26-137.81) 136.31	(4.81-4.95) 4.87
Generic	(32.98-35.89) 33.88	(1.91-1.99) 1.96	(202.22-206.31) 204.19	(5.29-5.84) 5.44
Level of significance	$P \geq 0.05$	$P \geq 0.05$	$P \leq 0.05$	$P \geq 0.05$

In three of the four parameters, there were no significant differences between patients in Groups 1 and 2 (Table 2), namely, for maximum drug concentration, period of achieving maximum drug concentration in blood plasma, and period of the drug retention in blood plasma. The only difference was in the area under the pharmacokinetic curve. Thus, this value was slightly lower ($p \leq 0.05$) in the original drug (Group 1). A significant difference between groups ($p \leq 0.001$) was observed 1 hour after administration. The relevant value was 29.84 ng/1 ml for the original drug and 19.01 ng/1 ml for the generic. In other words, the original drug demonstrated higher adsorption properties, which may be due to the different compositions of excipients used in the two medications under study (Figure 1).

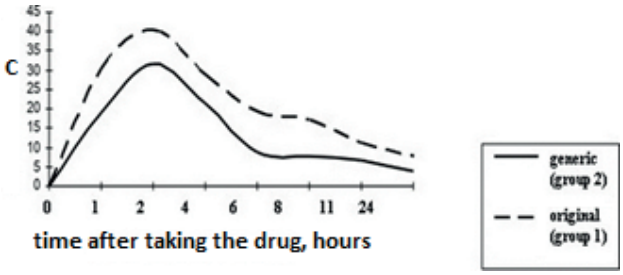

Figure 1. Indicators of the concentration-time curve for patients of Groups 1 and 2 after administration of the drug for 1 – 24 hours. C – concentration (ng / ml, Figures 1-2).

This correspondence was also retained in the following hours after drug administration, amounting to 38.2 ng/1 ml ($p \leq 0.001$) after 2 hours, 36.6 ng/1 ml ($p \leq 0.6$) vs. 26.5 ng/1 ml ($p \leq 0.001$) after 4 hours. Thus, high values of the concentration-time curve in favor of the original drug were maintained throughout the study period. Even after 24 hours, the concentration of the generic drug was 5.1 ng/1 ml vs. 9.2 ng/1 ml for the original drug ($p \leq 0.001$). Thus, the maximum values of the concentration-time curve for both drugs occur in the time interval of 2 hours after administration.

The maximum concentration values of both drugs were reached after 6 hours (Figure 2). Figure 2 shows significant differences between the drugs in all time intervals in terms of the main active ingredient concentration.

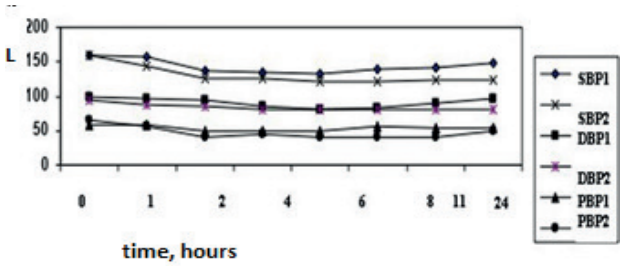

Figure 2. Changes in enalapril concentration in both groups of patients within 1-24 hours after a single dose of the drug.

At 2 hours after administration, these values were 10 ng/1 ml for the generic and 2.5 times higher for the original drug, amounting to 25.0 ng/1 ml ($p \leq 0.001$). At 6 hours, these Figs differed, even more, amounting to 81 ng/1 ml vs. 37 ng/1 ml ($p \leq 0.0001$), respectively. The results show that the processes of circulation, elimination, and distribution of the drug through the body differ essentially (by a factor of 2-4) between the original drug and the generic. For elderly patients, an increase in the retention time of the active drug substance in blood plasma is typical as well, which may be a consequence of the decreased metabolic activity in the liver.

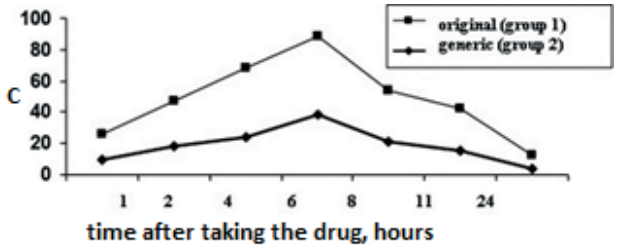

Figure 3. Blood pressure lowering rates (axe L, in mm Hg) in patients of both groups 1 to 24 hours after a single drug dose. (*Legend: SBP - systolic blood pressure, DBP - diastolic blood pressure, PBP - pulse blood pressure; 1, 2 - patient group* numbers).

These features are worth considering when enalapril is used to treat hypertension in elderly patients.

Pharmacodynamics of Original and Generic Enalapril

Figure 3 shows the features of changes in systolic, diastolic, and pulse blood pressure levels during a single oral administration of the original and generic enalapril. Pulse blood pressure is considered in the study as it may reflect the likelihood of cardiovascular events. Figure 3 shows that the more time elapsed after medication administration, the greater differences in systolic and diastolic blood pressure levels are observed. Thus, in the period of 8 – 24 hours, systolic pressure levels varied significantly between the two groups ($p \leq 0.05$). For diastolic pressure, differences were significant between groups in the period of 11–24 hours ($p \leq 0.05$) and for pulse pressure – in 8-11 hours ($p \leq 0.05$).

Correlation analysis showed that maximum drug concentration depended on hemodynamic parameters (Figure 4). In particular, for the concentration of the original enalapril drug 6 hours after oral administration, the correlation was -0.93 for systolic blood pressure, -0.52 for diastolic pressure, and -0.43 for pulse blood pressure. Differences were significant at $p \leq 0.01$. For the generic drug, these correlation values were -0.41 for systolic pressure, -0.30 for diastolic pressure, and only -0.12 for pulse pressure. The likelihood level was still $p \leq 0.01$.

It has been confirmed that the effect of hypotension is preserved as a function of the maximum drug concentration and hemodynamic parameters. The relation is linear in nature. Furthermore, the blocking of the renin system was recorded. Thus, in Group 1, this index was 5.8 hours, and in Group 2, it ranged from 5.91 to 5.98 hours. As a result, the original enalaprilstrongly affectsthe lowering rate of blood pressure at the maximum concentration, while generic drug does not exhibit such a clear relationship.

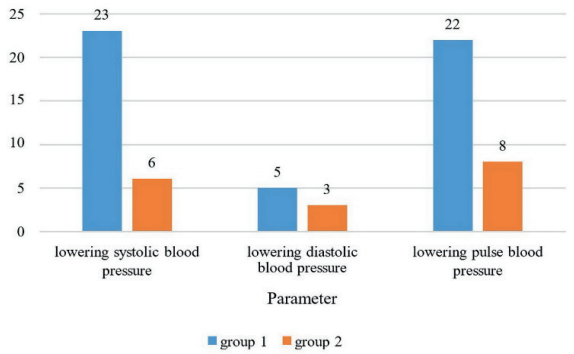

Figure 4. Pharmacodynamic parameters of original (Group 1) and generic (Group 2) enalapril after a single dose.

Two weeks after commencing treatment, the generic dose in Group 2 was doubled, and hydrochlorothiazide (12.5 mg daily dose) was added to all patients. Patients in Group 2 (15 patients) received chlorothiazide at the same dose. A sustained effect of blood pressure lowering was achieved over 4 weeks of monotherapy with the original drug in 50 patients of Group 1 ($p \leq 0.001$) and in 22 patients undergoing the combined therapy. In Group 2, the effect of polytherapy was 100% ($p \leq 0.001$). At the same time, unpleasant side effects such as a dry cough were not recorded in either group.

Multivariate analysis

The calculations were based on the Kaplan-Meier method. For Group 1 (monotherapy), the effect was 0.50. For patients in this group with combined therapy, the effect was 0.78. For Group 2, the effect of polytherapy was 1, i.e., the most pronounced. Thus, the inclusion of several medications in the therapy demonstrated greater effect compared to monotherapy.

Calculation of the post-factum sample size

At p 0.05, a sampling error was 6.95. Sufficient sample size is considered 199 patients, which corresponds to the sample size in this study (= 200).

Discussion

Due to the overall aging of the population in most developed countries, the AH as an age-related disease is increasingly common [19]. Therefore, there is an ongoing search for new therapies while taking into account the peculiarities of the body's metabolism in old age, as well as pharmacodynamics and pharmacokinetics of the drugs [20]. In modern cardiology, one of the problematic areas is the tactic of selecting effective drugs with a pronounced hypotensive effect in the long term [21]. The study of pharmacokinetics and pharmacodynamics of antihypotensive drugs, including ACE inhibitors, remains relevant since their effect varies significantly in people of different age groups [22]. In modern medicine, numerous drugs available in different countries are classified not as original but as generic drugs [23,24]. Generics tend to be cheaper than the original, and they're fairly numerous. As a result, physicians may very often have difficulty choosing an effective treatment tactic [25]. This study demonstrated the original drug's greater efficacy, which is supported by other data [26].

A well-known drawback of research projects to determine the bioequivalence of generics to the original drug is that such studies involve healthy young people and individuals. Age factor is not taken into account [27]. Perhaps this is why the statistics showed worse results for generics than for the original enalapril. Therefore, a very different effect from generics compared to the original in elderly and senile patients can be expected. An analysis in terms of pharmacoeconomics showed that in the long-term therapy, the original enalapril cost is still lower than that of the generics [12]. According to the findings of this work and other data, generics need to be administered in a twice-daily dosing regimen involving 3 or 4 drug components. For the original drug, a single daily dosage schedule consisting of two components is sufficient [12].

An unpleasant effect of the first dose of ACE inhibitors, particularly when combined with diuretics, is hypotension. Hypotension is typically asymptomatic, but a small share of patients, mainly those diagnosed with heart failure, may experience such effects as hypoperfusion of the heart, brain, and kidneys. Among patients suffering from heart failure, the proportion of these cases does not exceed 10% [10]. Patients who have been so diagnosed were not included in this study. Seniors can also develop a pronounced effect of ACE inhibitors if they are diagnosed with malignant hypertension [22]. Patients with this diagnosis were also excluded from the study. The same applies to patients with recent myocardial infarctions.

Conclusion

Deviations in the pharmacokinetics of both original and generic enalapril have been observed in older patients (over 75 years). There was a statistically significant difference in the pharmacokinetics for the two drugs. When treating AH with generic drugs, consideration must be given to such factors as plasma concentrations and the effects of lowering blood pressure.

In addition, there was a difference in the time interval. Thus, with a longer time interval, there were growing differences in systolic, diastolic, and pulse blood pressure levels. While significant differences were obtained for systolic pressure for a period of 16 hours (8 to 24 hours, $p \leq 0.05$), this period was 13 hours for diastolic pressure (11 to 24 hours, $p \leq 0.05$), and only 3 hours for pulse pressure (8 to 11 hours, $p \leq 0.05$). Significant differences were noted between the maximum drug concentration and hemodynamic parameters. After 6 hours, the correlation coefficient for the original drug was -0.93 for systolic blood pressure, -0.43 for diastolic, and -0.52 for pulse pressure. All correlations are significant at $p \leq 0.01$. The correlation is much weaker for the generic drug, amounting to -0.41 for systolic, -0.30 for diastolic, and only -0.12 for pulse pressure ($p \leq 0.01$). It indicates that generic drugs are much less effective than hypotensive drugsthan the original enalapril. Therefore, considering the body characteristics in older people, the original enalapril is recommended when choosing therapy tactics.

List of Abbreviations

AH	arterial hypertension
c	maximum drug concentration
tmax	period of reaching maximum drug concentration in blood plasma
tconc	period of drug retention in the blood plasma
S	values of area under the pharmacokinetic curve
ACE	angiotensin-converting enzyme inhibitor
ASCOT	Anglo-Scandinavian Cardiac Outcomes Trial
SBP	systolic blood pressure
DBP	diastolic blood pressure
PBP	pulse blood pressure

Ethics Approval and Consent to Participate

The authors declare that the work is written with due consideration of ethical standards. The study was approved during the meeting of the Ethics Committee of the Moscow State University Lomonosov (Protocol No. 459). Informed consent was signed by participants.

Human and Animal Rights

The research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki.

Research Involving Plants

Not applicable

Consent for Publication

Not applicable

Availability of Data and Materials

The data supporting the findings of the article is available within the article.

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Conflict of Interest

Authors declare that they have no conflict of interest.

Acknowledgements

Not applicable

Authorship

All authors contributed equallyto the concept, research question and study design, and data collection or processing.All authors have read the manuscript before submission.

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