Progress of Amlodipine and Enalapril in the Treatment of Hypertension

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Keywords: Hypertension, Amlodipine, Enalapril, Pharmacology, Origin, Delivery, Pharmacoeconomic.

Abstract: BACKGROUND: Hypertension is a long-term chronic disease that has a tremendous negative impact on people's lives, and its prevalence varies by gender, region, and ethnicity. Calcium channel blockers (CCBs) and angiotensin-converting enzyme inhibitors (ACEIs) are widely used among the first-line antihypertensive agents. CONTENT: The type, epidemiology, pathology, and therapeutic means of hypertension were analysed. The origin of amlodipine, a representative drug of CCBs, and enalapril, a representative drug of ACEIs for the treatment of hypertension was analysed, and their latest progress in pharmacological effects, delivery, combined use, and pharmacoeconomics were summarized and compared. RESULTS: Amlodipine is more suitable for patients who need myocardial protection, and enalapril is more suitable for patients with ventricular hypertrophy. The combination of the two drugs provides better protection for the cardiovascular system. Both drugs are primarily administered orally, but different effects can be achieved by using different dosage forms. Amlodipine is more affordable than enalapril and has a larger market.

1 INTRODUCTION

Heart and cardiovascular and cerebrovascular diseases are the number one cause of death for people in developed countries and 44% of people in China died because of heart and cardiovascular and cerebrovascular diseases (Bai, et al. 2018). Therefore, research on the cardiovascular system has become the focus of attention of scientists in the fields of medicine and pharmacy from all over the world. Among them, hypertension, as an important factor in increasing the risk of cardiovascular disease has attracted much attention.

This article analyzed s the typology, epidemiology, pathology, and treatment of hypertension in the first place. Hypertension, also known as systemic arterial hypertension, is manifested by a long-term increase in systemic arterial blood pressure. Blood pressure is usually expressed as the ratio of the systolic pressure (that is, the pressure of the arterial wall when the heart is contracting) to the diastolic pressure (the pressure when the heart is in diastole) (Oparil, et al. 2018). As shown in Table 1, hypertension can be divided into the following stages. Hypertension is a long-term chronic disease that has a great negative impact on people's lives. And because hypertension is difficult to cure, the vast majority of hypertensive patients need long-term medication or even lifelong medication (Tsioufis, and Thomopoulos 2017). Hypertension is still an unsolved medical problem, and therefore hypertension research still needs to be carried out in depth. The analyzation of hypertension in this paper provides some material to support and enlighten the subsequent related studies.

Table 1: Categories of BP in Adults

Blood Pressure Category	Systolic blood pressure (SBP)		Diastolic blood pressure (DBP)
Normal	<120mmHg	and	<80mmHg
Elevated	120~129mmHg	and	<80mmHg
Hypertension			
Stage 1	130~139mmHg	or	80~89mmHg
Stage 2	≥140mmHg	or	≥90mmHg

The article analysed the origins of amlodipine, a representative drug of the CCB class for the treatment of hypertension, and enalapril, a representative drug of the ACEI class, to sort out the history of drug development and make it clearer and more definite. The pharmacological effects, routes of administration, co-administration, and the latest progress of pharmacoeconomics of the two drugs are also

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summarized and compared. It provides a comprehensive reference for the selection and comparison of drugs for the treatment of hypertension, and lays the foundation for the in-depth study of the pharmacological effects and targets of action of these two drugs.

2 HYPERTENSION

2.1 Types of the Hypertension

The cause of the vast majority of hypertension is unknown, called essential hypertension(EH); a small amount of hypertension has a cause that can be checked, called secondary hypertension(SH).

The etiology and mechanism of essential hypertension are still unclear, but with the continuous deepening of research, some people believe that essential hypertension is not a disease but a syndrome. A major manifestation of this syndrome is increased blood pressure (Manosroi, and Williams 2019). The emergence of essential hypertension is not caused by a single factor. It is more caused by the cumulative effect of multiple factors. Studies have supported this view, such as genetic inheritance and long-term high-salt diet. Habits, the influence of the microbiota in the body on blood pressure (Chakraborty, et al. 2020).

Common causes of secondary hypertension include obstructive sleep apnea (OSA), renal parenchymal disease, renal artery stenosis, and primary hyperaldosteronism (PA) (Rimoldi, Scherrer, and Messerli 2014). It is worth mentioning that many patients with secondary hypertension still have hypertension symptoms after removing the secondary causes. This indicates that many patients with secondary hypertension may be accompanied by essential hypertension or irreversible remodeling of blood vessels.

2.2 Epidemiology of the Hypertension

In China, the symptoms of hypertension are SBP ≥ 140mmHg and DBP ≥ 90mmHg. According to the report paper, the prevalence of hypertension in China is increasing, and it is characterized by 1)higher rates of hypertension in men than in women, 2)higher prevalence in the north than in the south, 3)higher prevalence in rural areas than in urban areas, 4)and differences in prevalence between ethnic groups (J Geriatr Cardiol 2019). As of 2015, the awareness rate of patients with hypertension was only 55.7%, the treatment rate was less than 50%, and only 20% of the patients treated had their blood pressure under control (Wei, et al. 2021).

Globally, about 31.1% of adults suffer from hypertension, and the incidence in developed countries is higher than that in developing countries. There is an age difference in hypertension, that is, as the age increases, the incidence increases, as shown in Table 2.

Table 2: Age-specific and age-standardized prevalence estimates and absolute numbers of men and women with hypertension in high-income and low- and middle-income countries in 2010 (Mills, et al., 2016)

Age, years	Prevalence % (95% CIs)				Absolute Numbers in Millions (95% CIs)			
	High-income countries		Low- and middle-income countries		High-income countries		Low- and middle-income countries	
	Men	Women	Men	Women	Men	Women	Men	Women
20-29	10.7 (5.9, 15.5)	4.3 (1.9, 6.6)	15.2 (11.5, 18.9)	10.4 (7.0, 13.7)	10.0 (5.5, 14.4)	3.7 (1.7, 5.8)	77.1 (58.3, 96.0)	50.6 (34.3, 66.9)
30-39	18.5 (14.1, 22.9)	9.1 (6.3, 12.0)	22.1 (17.7, 26.5)	17.4 (13.3, 21.6)	17.4 (13.3, 21.5)	8.2 (5.6, 10.8)	90.2 (72.2, 108.3)	69.6 (53.0, 86.2)
40-49	31.0 (26.8, 35.3)	22.0 (18.5, 25.5)	31.2 (26.4, 36.0)	30.6 (25.7, 35.6)	29.0 (25.0, 33.0)	20.5 (17.2, 23.8)	108.0 (91.4, 124.6)	103.9 (87.3, 120.6)
50-59	48.5 (43.6, 53.4)	41.0 (36.3, 45.7)	43.0 (37.9, 48.1)	47.2 (41.8, 52.6)	40.4 (36.3, 44.5)	35.9 (31.8, 40.1)	106.1 (93.5, 118.7)	115.7 (102.5, 128.9)
60-69	60.8 (56.8, 64.8)	60.9 (56.7, 65.0)	55.3 (50.1, 60.6)	61.9 (56.2, 67.7)	36.4 (34.0, 38.8)	40.8 (38.0, 43.5)	76.4 (69.1, 83.6)	90.6 (82.2, 99.0)
≥70	73.6 (70.0, 77.3)	77.5 (73.9, 81.0)	65.6 (60.6, 70.7)	74.7 (69.6, 79.7)	41.1 (39.0, 43.1)	65.5 (62.5, 68.4)	62.4 (57.5, 67.2)	88.5 (82.5, 94.5)
Overall	31.6 (29.6, 33.6)	25.3 (23.9, 26.7)	31.7 (29.7, 33.6)	31.2 (29.3, 33.1)	174.2 (165.3, 183.2)	174.7 (167.2, 182.1)	520.1 (485.6, 554.7)	518.8 (485.7, 552.0)

Values are percentages and 95% confidence intervals

High blood pressure is often not a fatal factor, but high blood pressure can cause organ damage, increase the risk of other cardiovascular diseases, and may have complications. Some complications of hypertension include renal failure, stroke, heart failure, coronary heart disease, etc., and most of these complications can cause death and disability (Flack, et al. 2003).

2.3 Pathology of the Hypertension

The basic factors that form arterial blood pressure are cardiac output and peripheral vascular resistance. The former is affected by heart function, return blood volume, and blood volume and the latter is mainly affected by the tension of the arterioles. The sympathetic nervous system and the renin-angiotensin system (RAS) regulate the above two factors to control blood pressure within a certain range.

2.4 Treatment of the Hypertension

At present, the treatment of hypertension advocates comprehensive treatment, that is, non-drug treatment and drugs are combined to control the patient's blood pressure.

Non-drug treatment is the change in the patient's living habits to control risk factors. This method advocate reducing sodium and salt intake, reasonable dietary arrangements, regular exercise, quitting smoking and drinking, and maintaining a good mood (J Geriatr Cardiol 2019).

In terms of drug treatment, currently, diuretics, calcium channel blockers, β receptor blockers, angiotensin converting enzyme inhibitors (ACEI), AT_1 receptor blockers, which are widely used or called first-line antihypertensive drugs, are widely used medicine. Clinical treatment of hypertension often adopts combination medications to reduce the damage to the patient's target organs and reduce complications (Tsioufis, and Thomopoulos 2017).

3 DESCRIPTION OF CHEMICAL STRUCTURES OF DRUGS

3.1 Structure and Nomenclature

3.1.1 Structure and Nomenclature of amlodipine

2D Structure: 3D Structure:

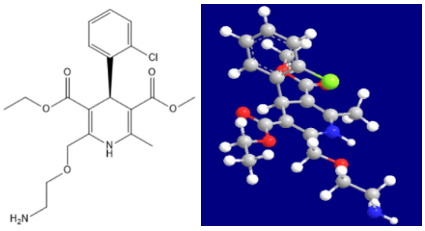

Figure 1: 2D and 3D structures of amlodipine.

The figure 1 shows the 2D and 3D structures of amlodipine. The amlodipine contains a benzene ring and a dihydropyridine ring, from the 3D structure can be seen that the two rings are not co-plane, but in a state perpendicular to each other. Dihydropyridine ring 3, 5-bit replacement group is different, so C4 is the stereoscopic center, and the activity of S configuration is stronger than R configuration (Coelho, et al. 2021).

Nomenclature:

The IUPAC Name of amlodipine is 3-O-ethyl 5-O-methyl 2-(2-aminoethoxymethyl)-4-(2-chlorophenyl)-6-methyl-1,4-dihydropyridine-3,5-dicarboxylate. This drug has many brand names in the market, such as Amlobenz, Azor, Caduet, Consensi, Dafiro, Exforge, Exforge Hct, Katerzia, Lotrel, Norvasc, Prestalia, Tribenzor, Twynsta, Viacoram. Clinical drugs amlodipine maleate and amlodipine besylate are widely used.

3.1.2 Structure and Nomenclature of enalapril

2D structure: 3D Structure:

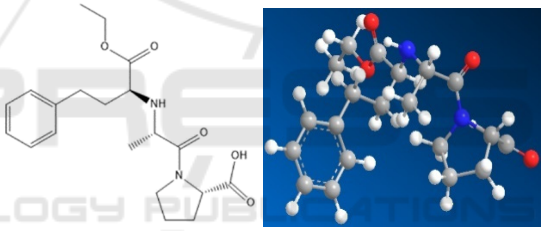

Figure 2: 2D and 3D structures of enalapril

The figure 2 shows the 2D and 3D structures of enalapril. The structure of enalapril contains a benzene ring, tetrahydropyrrole ring, carboxyl group, carbonyl group, an ester bond, and other structures. There are two chiral carbon atoms in the structure.

Nomenclature:

The IUPAC Name of enalapril is (2S)-1-[(2S)-2-[[(2S)-1-ethoxy-1-oxo-4-phenylbutan-2-yl]amino]propanoyl]pyrrolidine-2-carboxylic acid. This drug has three brand names on market, Epaned, Vaseretic, and Vasotec.

3.2 Chemical and Physical Properties

3.2.1 Chemical and Physical Properties of amlodipine

The molecular formula is $C_{20}H_{25}ClN_2O_5$, this drug is a small molecule drug. Its molecular weight is 408.9, solid, slightly soluble in water. The pK_a of

amlodipine is 9.4(amine)

3.2.2 Chemical and Physical Properties of enalapril

The molecular formula of enalapril is $C_{20}H_{28}N_2O_5$, this drug is a small molecule drug. Its molecular weight is 376.4, solid, Its solubility in water is 1.64×10^4 mg/L at 25 °C. The pKa of enalapril $pK_a1 = 3.0$ (carboxylic acid) and $pK_a2 = 5.5$ (secondary amide).

4 DISCUSSION OF DRUG PHARMACOLOGY

4.1 Origin and History of Drugs

4.1.1 Origin and history of Amlodipine

The study of calcium channel blockers on the cardiovascular system began around the 1960s. Amlodipine is the third generation dihydropyridine calcium channel blocker, which is modified from the first marketed dihydropyridine CCB nifedipine. Nifedipine was launched in 1975 and has been effective in controlling hypertension since it was launched. Compared with nifedipine, amlodipine has a long-lasting and stable lowering of blood pressure. It has become a once-a-day antihypertensive drug, which greatly improves the compliance of hypertensive patients (Burges, and Moisey 1994). Amlodipine can also reverse left ventricular hypertrophy (Lu, et al. 2016), especially for patients with hypertension and left ventricular hypertrophy.

4.1.2 Origin and History of Enalapril

In 1971, teprotide, the first active substance with an inhibitory effect on angiotensin converting enzyme, was isolated from the venom of a Brazilian snake. However, the oral administration of teprotide was ineffective, so it was necessary to find a more stable structure. Inspired by the inhibitor of carboxypeptidase A (an exopeptidase containing zinc ion active center, which was thought to be similar to ACE at that time) (Cushman, et al. 1982), succinylproline was synthesized. The product had a certain inhibitory effect on ACE, but its activity was low. To further increase the inhibitory activity, succinylproline was structurally modified by adding chiral carbon and replacing carboxyl with sulfhydryl. Surprisingly, this structural transformation increased the inhibitory effect by 2000 times (Cushman, and Ondetti 1991). This is the first ACEI drug captopril, which was listed by Squibb in 1981.

But then captopril was reported to have serious adverse reactions, such as proteinuria and taste loss. These adverse reactions were related to the sulfhydryl group contained in its structure (Jaffe 1986). Therefore, to eliminate these adverse reactions, the structure of captopril was modified α- Amphetamine replaces sulfhydryl group and is made into monoethyl ester as a prodrug (Patchett 1984). After enalapril enters the body, it can be metabolized into Enalapril to exert its efficacy, which was later listed by Merck in the United States.

4.2 Description of Drug Targets and How Their Function is Affected by the Drugs

4.2.1 Pharmacology of Amlodipine

Calcium ion plays an important role in the excitation-contraction coupling of the myocardium and vascular smooth muscle. The higher the concentration of calcium ions entering the cell, the stronger the contractility of the myocardium and vascular smooth muscle (Bers 2014). The entry of calcium ions into cells mainly depends on the calcium channels on the cell membrane. Calcium channels play an important physiological role in the body and can be divided into many subtypes (Zamponi, et al. 2015). The calcium channels distributed in the cells of the cardiovascular system are mainly L-type calcium channels.

Amlodipine is the third generation dihydropyridine (DHP) calcium channel blocker (CCB). Dihydropyridine drugs mainly inhibit L-type Ca2 + voltage-gated calcium channels widely distributed in the cell membrane of the cardiovascular system (Gao, and Yan 2021), prevent calcium influx, and inhibit the contractility of myocardium and vascular smooth muscle. In this way, the myocardial contractility is weakened, the heart rate is slowed down, the cardiac ejection is reduced, and the arterial blood pressure is reduced.

The calcium ion channel consists of α1 subunit that determines their characteristics and α2, δ, β, γ subunits help regulate the function of calcium ion channels (Catterall 2011). Calcium channel blockers can combine with calcium ion channels when α1 is in subunit inactivate condition to keep them inactive and reduce the flow of calcium ions into cells. According to Tang's research (Tang, et al. 2016), amlodipine can be combined with the dihydropyridine combined pockets of Ca_vAb, and the crystal structure of the

compound can well represent the state of Amlodipine regulate calcium channels, as shown in the Figure 3. Unlike non-dihydropyridine calcium channel blockers (e.g. Verapamil, Diltiazem), dihydropyridine drugs do not limit the internal flow of calcium ions by blocking pores but act as a gated regulator (Catterall, and Swanson, 2015).

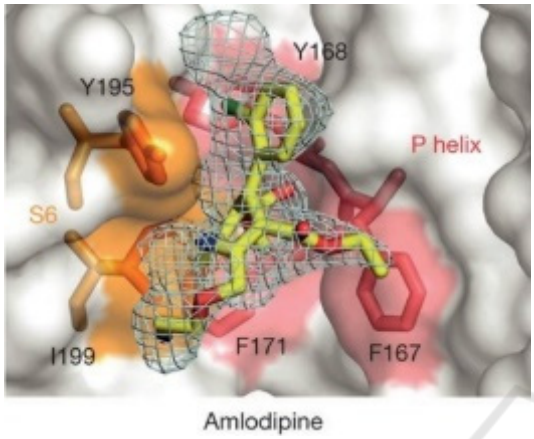

Figure 3: Crystal Structure of Compound of Amlodipine and Ca_VAb (Tang, et al. 2016).

The above is the traditional and recognized blood pressure reduction mechanism of amlodipine. In addition, recent studies have shown that amlodipine can also regulate arterial blood pressure in other ways. For example, amlodipine can inhibit the growth of vascular smooth muscle, regulate phenotypic conversion and reduce arterial blood pressure (Fang, et al. 2019, Stepien, et al. 1998).

4.2.2 Pharmacology of Enalapril

Enalapril is an antihypertensive drug that acts on the renin angiotensin system (RAS). It belongs to the angiotensin converting enzyme inhibitor (ACEI). The mechanism of ACEI lowers blood pressure is shown in figure 4.

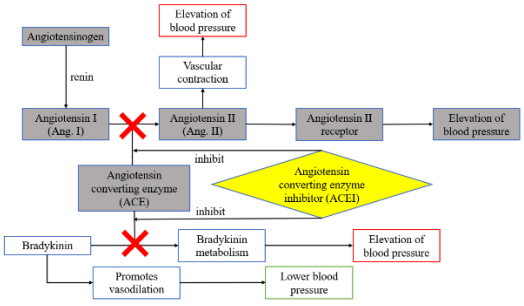

Figure 4: The mechanism of ACEI lowers blood pressure.

The renin angiotensin system (RAS) is an important system of body fluid regulation in the human body. It plays an important role in maintaining the stability of cardiovascular function and the balance of body fluid and electrolytes. However, excessive activation of RAS will lead to pathological phenomena such as hypertension and congestive heart failure (Forrester, et al. 2018). Therefore, a major idea for the treatment of hypertension is to down-regulate the over-excited RAS.

Renin is a protease synthesized and secreted by renal near globular cells. It can hydrolyze angiotensinogen (a polypeptide) into angiotensin I (a decapeptide molecule) (Fyhrquist, and Saijonmaa 2008). Angiotensin I has no obvious biological activity and has no obvious contractile effect on the heart and vascular smooth muscle (Li, et al. 1979).

Angiotensin converting enzyme (ACE) can catalyze the conversion of angiotensin I (Ang I) to angiotensin II (Ang II). Angiotensin II is the strongest vasoconstrictor in the angiotensin family, and it is a polypeptide substance. It can act on the AT1 receptors of the myocardium and vascular smooth muscle cells to directly constrict blood vessels and cause an increase in blood pressure (Peach, and Dostal 1990). In addition, Ang II can also promote the secretion of norepinephrine and aldosterone, thereby promoting the effect of sympathetic nerves on blood vessels, increasing the reabsorption of sodium ions and water, increasing blood volume, and leading to increased blood pressure (Schlaich, et al. 2005, Xanthakis, and Vasan 2013, Yatabe, et al. 2011).

When ACE is combined with ACEI, it can make ACE lose its catalytic activity, reduce the production of AngII, and relax blood vessels, thereby lowering blood pressure. In addition, ACEI can also enhance the effect of bradykinin (a substance that promotes vasodilation), make it accumulate, and lower blood pressure (Tom, et al. 2002).

4.3 Mode of Delivery

4.3.1 Delivery of Amlodipine

Amlodipine can be administered in many ways. Different modes of administration have their unique characteristics and adapt to the condition or disease severity.

Amlodipine can be salted with benzenesulfonic acid and maleic acid and administered orally. Tablet is the most common oral dosage form in the market. Although there are great differences in the activity of S- and R- configuration, there is no significant difference in the clinical effect between racemate and

amlodipine with single S-configuration, and there are no serious adverse reactions. Therefore, it is often administered in the form of a racemate (Park, et al. 2006). Oral instant amlodipine tablet is suitable for patients with dysphagia. After entering the mouth, this tablet disintegrates rapidly and is absorbed by the human body, but it has high requirements for the palatability of the tablet (Fukui-Soubou, et al. 2011). Layered tablets can release drugs at two different release rates. The effect of oral nanoemulsion on the target site is greatly improved compared with ordinary oral tablets (Chhabra, et al. 2011).

In addition to oral administration, there is also a form of intranasal administration. The biodegradable polymer hydroxypropyl guar is used to make amlodipine microspheres and penetrate the nasal mucosa (Swamy, and Abbas 2011).

4.3.2 Delivery of Enalapril

Enalapril is characterized as an oral prodrug, which is hydrolyzed and metabolized in the body to produce enalaprilat to produce pharmacological activity (Patchett 1984). The process of hydrolyze and metabolize is shown in Figure 5.

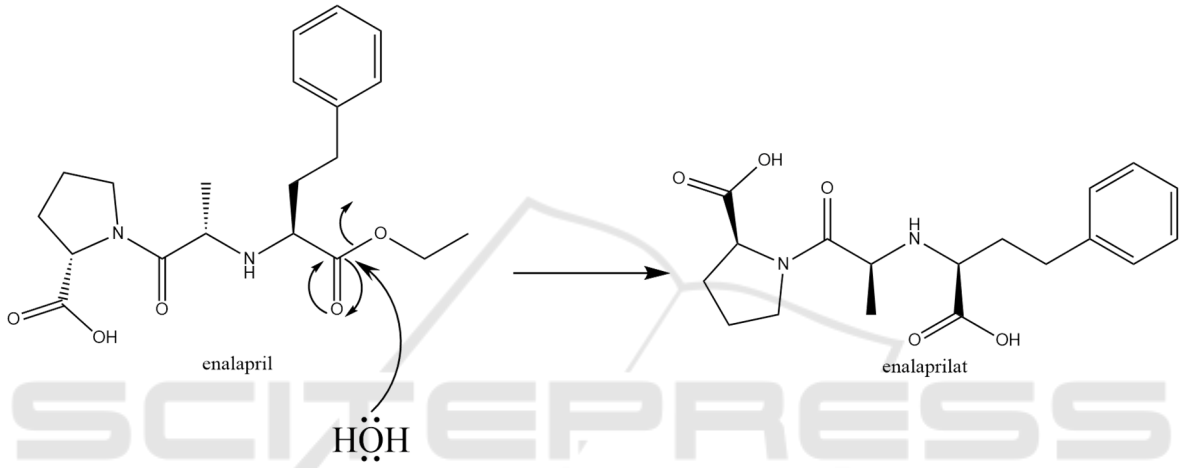

Figure 5: The prodrug enalapril is hydrolyzed and metabolized into enalapril in the body.

Enalapril is mainly administered orally. Enalapril maleate has a low degree of oral absorption, and the active form produced by first-pass elimination is greatly reduced. Existing studies have improved the bioavailability of oral enalapril in a variety of ways. Preparation of enalapril maleate suspended microspheres to control drug release (Abbas, and Alhamdany 2020). The cross-linked hard gelatin capsules are prepared, and the pulse drug delivery mode is designed to control the drug release rate (Tosha, et al. 2015). The oral mucosa is designed to adhere to the double-layer tablet to allow the drug to be absorbed through the oral mucosa to prevent the first-pass metabolism of the drug (Shah, Gadhethariya, and Shah 2014).

4.4 Comparison of Amlodipine and Enalapril

Amlodipine and enalapril are two drugs with different action mechanisms. Amlodipine belongs to dihydropyridine calcium channel antagonist, and enalapril belongs to angiotensin converting enzyme inhibitor ACEI. Because of their different mechanisms of action, they will have different effects on patients with hypertension.

From the perspective of pharmacological action, amlodipine can increase cardiac output, but enalapril has no significant change in cardiac output (Murdoch, and Heel 1991, Todd, and Heel 1986). Amlodipine increased the glomerular filtration rate, while enalapril did not affect the glomerular filtration rate (Murdoch, and Heel 1991, Todd, and Heel 1986). In known experiments, amlodipine has the effect of antiplatelet aggregation, but enalapril has no such effect (Hernández-Hernández, et al. 1999). Amlodipine can decrease the demand for oxygen of the myocardium and increase the protective effect on the myocardium (Murdoch, and Heel 1991). Enalapril can reverse the symptoms of cardiac hypertrophy in patients with left ventricular hypertrophy (Todd, and Heel 1986).

From the perspective of metabolism, the oral absorption of amlodipine is slow, reaching the peak of drug plasma concentration in 6 ~ 12 hours, and the oral absorption of enalapril is rapid, reaching the peak

in only one hour (Murdoch, and Heel 1991, Todd, and Heel 1986).

From the perspective of adverse reactions, the common adverse reactions of amlodipine include edema, muscle spasm, and so on (Galappatthy, et al. 2016). The common adverse reaction of enalapril is cough, which is a common adverse reaction in ACEI (Simon, et al. 1992).

From an application point of view, the combination of calcium channel antagonists and ACEI in the treatment of hypertension can better protect the cardiovascular system (Taddei 2015).

5 DISCUSSION OF DRUG ECONOMICS

5.1 Cost of Amlodipine and Enalapril

According to the data of clincalc.com, in 2018, the average total drug cost of amlodipine in the United States was $24.71 per prescription, the average out-of-pocket cost of patients was $4.79 per prescription, and the daily treatment cost (i.e., the average cost of each prescription divided by the number of days required for treatment, the same below) was $0.11/day. In the same year, the average total drug cost of enalapril maleate (the maleate of enalapril) in the United States was $42.88 per prescription, the average out-of-pocket cost of patients was $11.29 per prescription, and the daily treatment cost was $0.24/day (*Enalapril Maleate Drug Usage Statistics, United States 2021*). In contrast, the price of enalapril maleate is higher than that of amlodipine.

Compare the prices of amlodipine in China and the United States, unifying the purchase price of patients as USD per tablet. Only in terms of the price of tablets, the cost paid by Chinese patients with hypertension is 2.3 times that of American patients (Bai, et al. 2018).

5.2 The Number of Prescriptions and Sales

In 2018, the number of prescriptions for amlodipine exceeded 75 million, ranking fifth among prescription drugs in the United States, and it has maintained its top ten rankings in the past ten years, indicating that amlodipine has been used in huge amounts. The number of patients using amlodipine reached 15,851,641. Since 2008, the number of patients using amlodipine and the number of prescriptions has been slowly increasing (*Amlodipine Drug Usage Statistics 2021*).

Enalapril ranks 135th in the ranking of prescription drugs in the United States, with more than 5 million prescriptions and an estimated number of patients of 1.07 million. Unlike amlodipine, since 2008, the number of enalapril prescriptions and the number of patients has shown a downward trend, and the ranking of commonly used prescription drugs in the United States has also been declining in recent years (*Enalapril Maleate Drug Usage Statistics, United States 2021*).

Calcium channel blockers and β-blockers are the most prescribed drugs for hypertension. At the same time, in the treatment of elderly hypertensive patients, amlodipine is the most common drug, reaching 37% (Altaf, et al. 2014). In China, the defined daily dose of CCB in the five years from 2007 to 2015 accounted for about 42.8% of the five types of antihypertensive drugs, with an average annual growth rate of about 13.2%. In China, in the five years from 2007 to 2015, the defined daily dose of ACEI accounted for approximately 13.3% of the five types of antihypertensive drugs, with an average annual growth rate of approximately 1.4% (Xu, et al. 2015).

6 CONCLUSIONS

Hypertension is widely concerned all over the world because of its prevalence, difficulty to cure, and great harm. The pathogenesis of hypertension is not clear, but one of the possible trends in the research on the pathogenesis of hypertension is integration, that is, considering the cumulative effect of multiple factors, such as eating habits, gene inheritance, and microbiota. At present, the exploration of the possible pathogenic factors of hypertension is not exhaustive. However, based on the correlation between the known important pathogenic factors and the incidence rate of hypertension, a rough model can be established, which is important for preventing and controlling hypertension.

In the treatment of hypertension, amlodipine, a calcium channel blocker, and enalapril, an angiotensin converting enzyme inhibitor, have antihypertensive effects through different pharmacological effects. The research on the potential pharmacological mechanism of known drugs plays an important role in deeply understanding the pathogenesis and developing new targeted drugs. In recent studies on the discovery and research of new antihypertensive mechanisms of two drugs, amlodipine can regulate the configuration conversion of vascular smooth muscle to reduce blood pressure,

and the targets and real compounds that promote the configuration conversion are good research objects. For the antihypertensive drug market, the number of patients using amlodipine to reduce blood pressure is increasing year by year, which will promote the in-depth study of amlodipine. For other types of antihypertensive drugs, to occupy a larger market share, enterprises are required to optimize the production process and improve antihypertensive drugs and develop drugs or dosage forms with better efficacy, safety, and stability, and appropriate price.

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