Dean&Francis

ISSN 2959-409X

MS003702

Summary on Nifedipine and Captopril in Treating Hypertension

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Abstract:

Hypertension, a chronic disease, is one of the major health problems worldwide and needs to be controlled through education, early diagnosis and effective management. Two of the most prescribed medications for treating hypertension are nifedipine and captopril. The first chapter gives some background information on hypertension then, the mechanism and target of two drugs are explained. Both of them effectively lower the blood pressure of patients after. Nifedipine achieves this by blocking L-type calcium channels, while captopril produces the same effect by inhibiting the catalysis process of ATI to ATII of ACE. Next, the article moves on to review existing literature on cross-over comparison between nifedipine and captopril and concludes some common trends revealed by previous studies. It was found that nifedipine and captopril have approximately the same level of effectiveness but captopril tends to give less adverse reactions. In addition, synthesize methods of two drugs are also mentioned and compared.

Keywords:-Hypertension, Nifedipine, Captopril, Pharmacology, Chemical Synthesis.

1. Introduction

Hypertension describes a condition when the blood pressure is above 140(systolic) / 90(diastolic) mmHg, which is an extremely prevalent disease with a potential risk of leading to various serious complications like stroke and coronary heart disease if not well-controlled. According to the World Health Organization, an estimated 1.28 billion adults aged 30–79 years worldwide have hypertension, but 46% of them are unaware that they have the condition. Approximately only 1 in 5 adults with hypertension have it under control.

The specific pathogenesis of hypertension is not clear, but a number of factors increase the risk of hypertension. These include genetics, aging, and unhealthy lifestyle as a major cause comprising up to 80% of the hypertension occurrence. High-sodium, low-potassium diet, overweight and obesity, over-drinking, lack of exercise, and mental stress are all common incentives of hypertension.

Hypertension is normally classified as three levels with level 1 140-159/90-99mmHg, level 2 160-179/100-109mmHg and level 3>180/110mmHg. Patients with relatively low level often experience no symptoms but arrange of symptoms like chest pain, dizziness, breathing difficulties will emerge when hypertension is severe.

Using antihypertensive medications is the most com-

mon treatment of hypertension. There are several types of medications including diuretics, Beta-blockers, ACE inhibitors, Angiotensin II receptor blockers, calcium channel blockers, Alpha blockers, Alpha-2 receptor agonists, and vasodilators. In the following chapters, the author will explain and compare two widely used medicine, Nifedipine and Captopril.

2. Development and Pharmacology of Two Medications

In this section, the author will give an overview of both drugs and then explain their mechanism of action in detail.

2.1 Introduction and History

2.1.1 Nifedipine

Nifedipine, molecular formula $C_{17}H_{18}N_2O_6$, developed by Bayer, is a commonly prescribed antihypertensive drug belonging to the class of calcium channel blockers, and it is also used to treat angina pectoris.

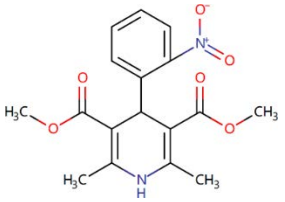

Figure 1. Nifedipine

Friedrich Bossert and Wulf Vater first proposed that dihydropyridines such as nifedipine may be effective as a medication of cardiovascular disease in 1964 [1]. In the following years, systematic research was carried out and literature *Pharmacology of 4-(2'-nitrophenyl)-2,6-dimethyl-1,4- dihydropyridine-3,5-dicarboxylic acid dimethyl ester (Nifedipine, BAY a 1040)* was published in 1972 [2]. Thereafter, nifedipine was granted FDA approval on 31 December 1981.

A typical prescription product of nifedipine is capsule, tablet and extended-release tablets dosage and all taken orally. According to FDA, the most frequently reported side effects in controlled studies were dizziness, flushing, headache and weakness with a proportion of 27%, 25%, 23% and 12%, respectively.

2.1.2 Captopril

Captopril is one of the primary choices for managing hypertension, which is the first angiotensin converting enzyme (ACE) inhibitor with molecular formula C9H-15NO3S.

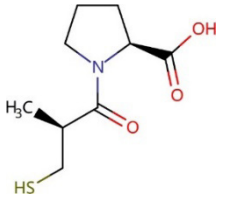

Figure 2. Captopril

Interestingly, captopril was discovered from snake venom. The initial idea came in 1971 when researchers David W. Cushman and Miguel A. Ondetti were studying snake venom peptides that inhibited ACE [3]. They hypothesized that an analog of a dipeptide could bind to the active site of ACE and hence act as an inhibitor and finally successfully synthesized captopril in 1975. Capoten (Captopril) was granted FDA approval on April 6, 1981.

Captopril is utilized through oral route of tablets with strength ranging from 12.5mg to 100mg per tablet. A range of adverse reactions was reported in clinical trials of about 7000 patients. The most common cases include rash, chest pain, loss of taste perception, cough and etc.

2.2 Mechanism and Target

2.2.1 Nifedipine

Nifedipine lowers blood pressure by blocking the L-type calcium channels (LTCCs / CaV1 Ca2+ Channels). L-type Calcium channels are also known as DHP-sensitive channels for the antagonistic or antagonistic effect of dihydropyridines on them. Another important characteristic of them is they exhibit generally large depolarizations to become activated, typically opening at potentials positive to −30 mV [4]. They serve in Ca^{2+} entry and trigger muscle contraction in cardiac, skeletal, and smooth muscles. Blocking the LTCCs through allosterically prevents the influx of Ca^{2+} into myocardial cells and smooth muscle cells, hence reducing peripheral arterial vascular resistance and dilating coronary arteries to produce antihypertensive effects.

LTCCs were found to have five subunits α1, α2, β, δ, and γ subunits [5]. What we are primarily focusing on is the α1 as the pore-forming subunit and the target of nifedipine as well as other kinds of dihydropyridines.

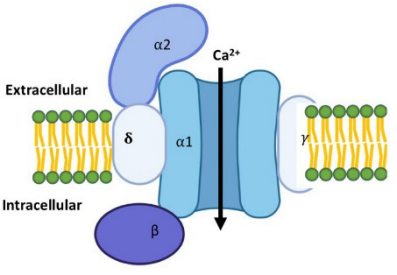

Figure 3. L-type Calcium Channel

ISSN 2959-409X

The polypeptide chain of α1contains four homologous repeats (I-IV) with six transmembrane segments (S1- S6) each. Segments S1-S4 in each repeat together form the peripheral voltage-sensing domains (VSDs)

In *Nifedipine binding to human Cav1.1 allosterically sets 3 out of 4 voltage sensors into their "relaxed state"* published in 2022, researchers demonstrated that the binding of nifedipine to the $Ca_V1.1$ pore region allosterically set the channel into a non-conducting stage by using voltage clamp fluorometry to investigate the effect of nifedipine on VSDs and found that the voltage dependence of VSD-I, VSD-II and VSD-III are severely altered [6]. The blockage of calcium channels in the vascular muscle cells will reduce the intracellular Ca^{2+} level, leading to the relaxation of vascular smooth muscle and vasodilation to reduce blood pressure.

2.2.2 Captopril

We already came to know that captopril is an ACE inhibitor, but to understand its mechanism of action we first need to take a look at the renin-angiotensin-aldosterone-system (RAAS), which is an intricate system consisting of hormones, proteins, enzymes and etc. responsible for blood pressure regulation.

RAAS regulation begins with the release of renin, a kind of protein, in the kidney by juxtaglomerular apparatus (JGA) triggered under three conditions. First, when baroreceptors detect low blood pressure, which is a kind of pressure-sensitive receptor located in afferent arterioles; second, low sodium level detected by macula densa cells at the distal convoluted tubules; third, β1 adrenoreceptors (another common target for antihypertensive medications) simulated by the sympathetic nervous system.

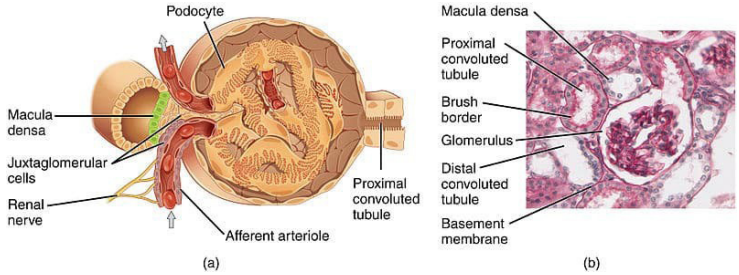

Figure 4. JGA and Maluca Densa Cells

Sequentially, renin converts angiotensinogen to angiotensin I (ATI), which could be considered an inactivated form of angiotensin (ATII). ATI is converted to ATII by angiotensin-converting enzyme (ACE) and causes a pressor effect through many means, like binding to receptors in the arterioles, leading to vasoconstriction. ATII also stimulates the release of aldosterone and antidiuretic hormone (ADH) in the adrenal gland as another core element of RAAS. These hormones increase the sodium level and water retention in the kidney to raise blood volume and blood pressure. Thus, preventing the production of ATII is the key, and captopril achieves this through competing with ATI for binding to ACE.

ACE was discovered in the 1950s, mainly responsible for conversion from ATI to ATII and the degradation of bradykinin. Over the years, other homologs of ACE that could convert ATII to AT (1- 9) were also discovered by researchers but were found to be captopril-insensitive [7]. Somatic ACE has C and N two domains and was often assigned with equivalent function which was not actually the case. In 2010, Kenneth E. Bernstein et al. monitored the blood ATI and renin levels of selective N-domain inactivated (N-KO) and C-domain (C-KO) inactivated mice and found that N-KO mice have normal levels of both factors [8]. Thus, they come to the conclusion that the C-domain is responsible for the majority of the conversion from ATI to ATII since these N-KO mice have the undisturbed function of the C-domain. Captopril competes with ATI for both active sites and was found to have a 3000 times greater affinity than ATI.

3. Comparison Between Nifedipine and Captopril

We already explained the distinct mechanism of action of nifedipine and captopril in the previous section, but as the two kinds of most widely prescribed antihypertensive medications, there are many other dimensions that we could take into consideration. In this chapter, the author would like to make a broad comparison of both drugs in terms of effectiveness, side effects, and synthesis process and try to make some suggestions on their clinical usage.

3.1 Effectiveness and Side Effects

Nifedipine and captopril both gained FDA approval in 1981; since then, they have been excessively studied, including plenty of them focusing on the cross-over comparison of their effectiveness and side effects.

In 1986, W W Klein, W Stuhlinger, and G Mahr conducted a cross-over study to investigate the antihypertensive effect of Nifedipine and captopril on 26 patients. Their results reflect that nifedipine tends to be more effective than captopril while the latter generally gives rise to fewer side effects since the study showed that 7 out of 26 captopril-treated patients showed no response while 3 of the 26 patients received nifedipine were non-responders and 7/26 captopril-treated patients, 22/26 nifedipine-treated patients reported side effects [9]. However, the sample size was relatively small, so we cannot be certain with this trend. Four years later, G Guerrera et al. carried out an investigation on 40 patients who received either 10 mg of nifedipine or 25 mg of captopril sublingually and found that 90% of the nifedipine group showed satisfactory blood pressure control with a significant reduction after 5 min while 80% succussed in captopril group and a significant reduction in blood pressure was shown after 10 minutes [10]. Furthermore, the antihypertensive effect lasted longer in the captopril group compared with the nifedipine group, which lasted six and four hours, respectively. A similar conclusion on the side effects of two medications was drawn in 1991 by Paolo Angeli et al. They conducted a randomized, single-blind clinical trial and found that both captopril and nifedipine are able to effectively lower blood pressure, but side effects occurred in 3 of the 10 nifedipine-treated patients, while none of the captopril counterparts reported any adverse reactions [11]. Thus, researchers suggested captopril to be prescribed as a safer choice. In the article *Sublingual nifedipine and captopril in hypertensive urgencies and emergencies.* Dadkar VN et al investigated the effectiveness of the same dosages of nifedipine and captopril [12]. Their findings were broadly similar to those of Guerrera G. et al. in 1990, but patients treated with nifedipine had a longer duration of antihypertensive effect than those treated with captopril. A recent study published in 2011 provided us with data from their testing on the action of Adalat® (nifedipine) (5 droplets) and captopril (25mg) on two random groups of 40 patients. For the Adalat® group, systolic blood pressure was reduced by 16% in the 20th, by 24% in the 40th, and by 28% in the 60th minutes. Captopril reduced blood pressure by 17%, 22.5%, and 27.6%, respectively [13].

Based on all the research mentioned above, we could observe a common trend that nifedipine tends to produce a relatively stronger quicker antihypertensive effect while captopril causes fewer adverse reactions among patients. Thus, nifedipine may be a preferable choice when treating emergency cases of hypertension, but captopril is generally safer for the long-term management and control of blood pressure. Notably, captopril cannot be used during pregnancy, and nifedipine is not suggested as well, especially during the first three months of pregnancy.

3.2 Synthesis Process

The most widely used synthetic methods for nifedipine are the Hantzsch method and the microwave synthesis method, in which the Hantzsch method uses methanol as a solvent and a reflux reaction using 2-nitrobenzaldehyde, methyl acetoacetate, and ammonium bicarbonate as starting materials. While the microwave method uses solvent-independent conditions, using 2-nitrobenzaldehyde, methyl acetoacetate, and methyl 3-aminocrotonate as raw materials, the synthesis is carried out by microwave radiation. In comparison, microwave synthesis has the advantages of shorter reaction time, easier operation, environmental friendliness, and a high yield; the yield reached 81.2% [14].

As for the industrial synthesis of captopril, one of the most traditional methods includes reacting 2- 2-methacrylic acid with thiolacetic acid, but this route exhibits a main disadvantage due to the use of thiolacetic acid, which causes harm to the environment. Some improved routes of synthesis were designed over the years, like reacting methacrylic acid with a hydrogen halide which eliminates the use of thiolacetic acid proposed by Doo H. Nam et al. in 1984 [15]. This synthesis method also possesses some drawbacks, like relative yield (28%) and the production of undesired 2R-enantiomer. Fortunately, researchers never give up on their quest to improve and optimize the synthesis of this vital drug. Better synthesis routes are constantly developed and produced. In *Summary of the Synthesis Route of Captopril (2011), Researchers have proposed an industrial preparation route for Captopril with good industrial application prospects*. This method has the merits of mild reaction conditions, high yield, high purity, and low pollution. The author believes that more and more superior versions of captopril synthesis will be designed in the future [16].

ISSN 2959-409X

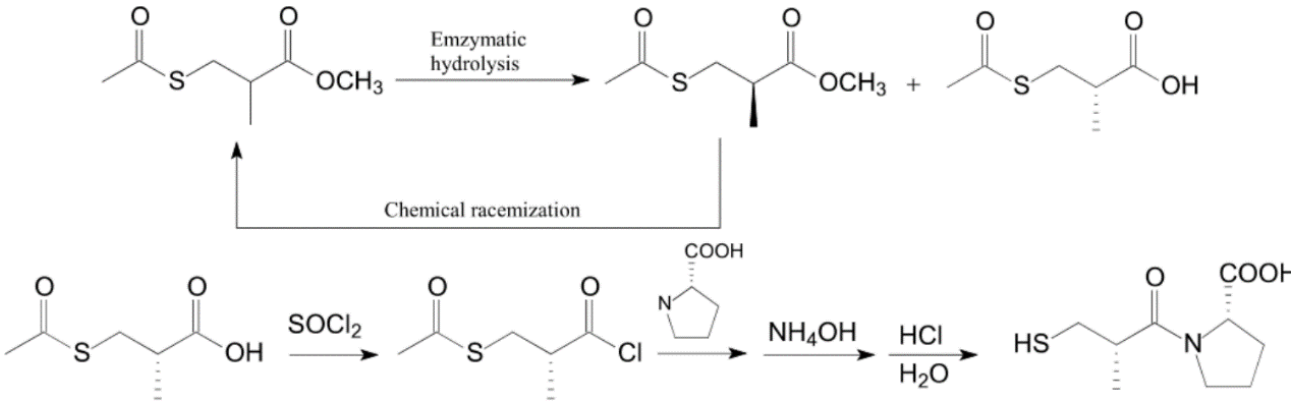

Figure 5. Synthesis Route of Captopril

Taken together, comparing the microwave synthesis method of nifedipine with the now commonly used synthesis method of captopril, the synthesis of nifedipine is environmentally and operationally superior because it avoids the use of organic solvents and has shorter reaction times and higher yields.

4. Conclusion

To briefly conclude, the article mainly focused on explaining the mechanism of action of two kinds of hypertensive medications-nifedipine and captopril, and made a rough comparison of them in the next section. The pharmacology of two drugs is explained in chapter two. Nifedipine is a kind of L-type calcium channel blocker that disturbs the influx of calcium ions into arterial muscle cells, hence reducing blood pressure. Captopril is a kind of ACE inhibitor and produces an antihypertensive effect by interfering with the RASS. Captopril competes with the binding site on ACE with ATI to prevent its conversion into ATII. Next, the author compares these two drugs in effectiveness, side effects, and synthesis process. According to studies published so far, nifedipine generally shows a similar antihypertensive effect, quicker onset of action, and simpler synthesis process but has a severe side effect compared to captopril. Based on all the information above, the author would suggest using nifedipine in emergent cases of hypertension and captopril in daily blood pressure management. Clinically, a combination of two drugs or other antihypertensive drugs is also used if a single medication is not effective enough.

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