Comparison of Enalapril and Atenolol Hypertension Drugs' Principle

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Abstract: This essay investigates two drugs that are both treatments for Hypertension, Enalapril and Atenolol, by researching and comparing their structures, mechanisms, cost, and side effects. As a result, it was found that even their mechanisms of action are different. What they do is a duplicate, simple thing. Enalapril and Atenolol inhibits something that is producing in the body, which can lead to Hypertension. Therefore, it can reduce blood pressure to the average level. In conclusion, Medicine is not as arcane as it looks. To be straightforward, Medicine is just something that can affect mechanisms in the body and is used to make various physical indicators to achieve usual standards. So that people won't have any health issues.

1 INTRODUCTION

Hypertension is a worldwide disease that leads to tons of deaths. After a long working period, Pharmacologists worldwide have discovered many types of medicine for hypertension such as ACE inhibitors, beta-blockers, Angiotensin II receptor blockers, and Calcium channel blockers. The following text talks about two drugs which count as ACE inhibitors (Enalapril) and beta-blockers (Atenolol). It tends to investigate drugs' principles and how the side effects cause the drugs' popularity.

In the work, I introduced and compared these two drugs' structures, mechanisms, costs, side effects, and popularity. I argued that side effects might be the main reason for their popularity by stating two research works done by other researchers. And at last, I state how simple the drug principle is.

2 OVERVIEW OF DISEASE

Blood pressure, also known as Hypertension, It's the pressure that blood gives to the wall of arteries (https://www.who.int/china/health-topics/hypertension). There are no specific symptoms for high blood pressure, but in the long-term having it, it may lead to other issues such as kidneys failure and heart diseases. The only way patients will know if they are weather-affected is to see a doctor for a physical examination.

There is used to have two numbers doctor will give as a result. For example 140/60. The first number is systolic blood pressure. It is the pressure when the heart is pushing or contracting blood. And the second number represents the pressure heart is relaxed and filled up with blood. It's called diastolic blood pressure.

Typically, healthy blood pressure for an adult is under 120/80. The first number is always higher than the second one. It's not a health concern. Here is a list of Hypertension and how're their numbers look. Table 1 shows different categories of blood pressure at different systolic and diastolic number.

- If the systolic number is higher than 140 and the diastolic number is higher than 90, this is just commonly Hypertension with no other heart risk factors

- If the systolic number is higher than 130 and the diastolic number is higher than 80, patients may have Hypertension with other heart risk factors, according to some providers

- If the systolic number is higher than 180 and the diastolic number is higher than 120. It's better to see medical care immediately.

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Table 1: Blood Pressure Categories (U.S. National Library of Medicine, 2021).

Pressure Category	**Systolic Blood Pressure**		**Diastolic Blood Pressure**
Normal	Less than 120	**and**	Less than 80
High Blood Pressure (no other heart risk factors)	140 or higher	**or**	90 or higher
High Blood Pressure (with other heart risk factors, according to some providers)	130 or higher	**or**	80 or higher
Dangerously high blood pressure - seek medical care right away	180 or higher	**and**	120 or higher

There are about 1.13 billion people affected by high blood pressure, and 2/3 of them live in a low, mid-income country. In 2015, one in four men and one in five women had Hypertension. There are about 270-million-people have high blood pressure in China. And only 13.8% is under control. Not everyone who has Hypertension can access treatment. Some primary care services are in the hard-to-reach area. They are not empowered to diagnose and treat high blood pressure to prevent life-threatening conditions (https://www.who.int/china/health-topics/hypertension); (https://www.who.int/news-room/fact-sheets/detail/hypertension).

There are many drugs used to treat Hypertension. Enalapril, Atenolol, Trandolapril, Ramipril, Lisinopril... In the following articles, Enalapril and Atenolol will be detailedly introduced.

3 DESCRIPTION OF DRUGS

Enalapril was patented in 1978, and it started to be used as Medicine in 1984. Its condensed chemical formula is C20H28N2O5. It's IUPAC name is (2S)-1-[(2S)-2-[[(2S)-1-ethoxy-1-oxo-4-phenylbutan-2-yl] amino] propanoyl] pyrrolidine-2-carboxylic acid (https://pubchem.ncbi.nlm.nih.gov/compound/Enalapril). It belongs to the ACE inhibitor drug class. Figure 1 and figure 2 shows Enalapril's 2D and 3D structure.

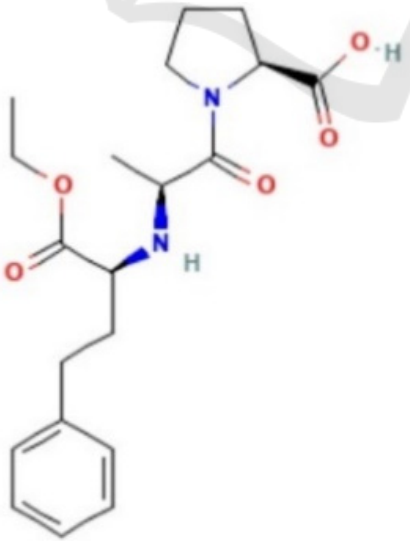

Figure 1: 2D Structure of Enalapril (https://pubchem.ncbi.nlm.nih.gov/compound/Enalapril).

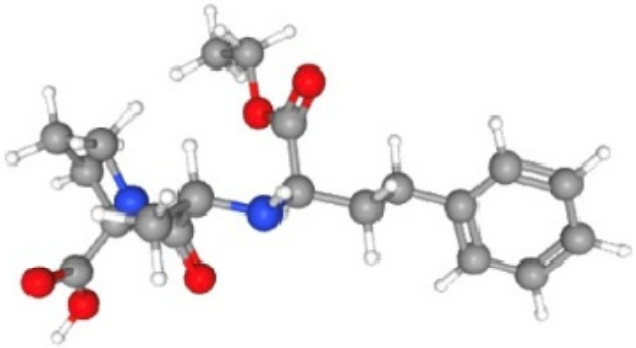

Figure 2: 3D structure of Enalapril (https://pubchem.ncbi.nlm.nih.gov/compound/Enalapril)

Enalapril is solid with a melting point around 143-144.5°C (https://pubchem.ncbi.nlm.nih.gov/compound/Enalapril). It is slightly soluble in water. Under the room temperature (25°C), 16.4g Enalapril can dissociate with one litre of water. It has a molarity of 0.04 M. It's stable under specific conditions. With the dilution of enalaprilat injection in 5% dextrose, 0.9% sodium chloride, 5% dextrose and 0.9% sodium chloride, 5% dextrose in lactated Ringer's, or Isoyte (R) E, Enalapril solution is stable for the next 24 hours at room temperature (American Society of Health-System Pharmacists, 2017). It's a dicarboxylic acid monoester. Enalapril has a $pKa1 = 2.3$ (carboxylic acid), $pKa2 = 3.4$ (carboxylic acid) and $pKa3 = 8.0$ (secondary amid) (Loftsson T, 2017). Table 2 shows its detailed properties.

Table 2: Enalapril chemical and physical properties (https://pubchem.ncbi.nlm.nih.gov/compound/Enalapril).

Property Name	Property Value	Reference
Molecular Weight	376.4	Computed by PubChem 2.1 (PubChem release 2021.05.07)
XLogP3	-0.1	Computed by XLogP3 3.0 (PubChem release 2021.05.07)
Hydrogen Bond Donor Count	2	Computed by Cactvs 3.4.8.18 (PubChem release 2021.05.07)
Hydrogen Bond Acceptor Count	6	Computed by Cactvs 3.4.8.18 (PubChem release 2021.05.07)
Rotatable Bond Count	10	Computed by Cactvs 3.4.8.18 (PubChem release 2021.05.07)
Exact Mass	376.199822	Computed by PubChem 2.1 (PubChem release 2021.05.07)
Monoisotopic Mass	376.199822	Computed by PubChem 2.1 (PubChem release 2021.05.07)
Topological Polar Surface Area	95.9 Å²	Computed by Cactvs 3.4.8.18 (PubChem release 2021.05.07)
Heavy Atom Count	27	Computed by PubChem
Formal Charge	0	Computed by PubChem
Complexity	519	Computed by Cactvs 3.4.8.18 (PubChem release 2021.05.07)
Isotope Atom Count	0	Computed by PubChem
Defined Atom Stereocenter Count	3	Computed by PubChem
Undefined Atom Stereocenter Count	0	Computed by PubChem
Defined Bond Stereocenter Count	0	Computed by PubChem
Undefined Bond Stereocenter Count	0	Computed by PubChem
Covalently-Bonded Unit Count	1	Computed by PubChem
Compound Is Canonicalized	Yes	Computed by PubChem (release 2021.05.07)

3.1 Atenolol

Atenolol was found out by a Scottish pharmacologist, James Black. He is the first man who used the beta-blocker for managing angina pectoris. He received Nobel Prize in 1958. Since then, Beta-blocker has quickly become popular. During the 1960s-1980s, It was investigated soon to be used in different types of cardiovascular diseases. It has a condensed molecular formula, C14H22N2O3. It is a beta-blocker (Drug Bank, 2021). Figure 3 and figure 4 shows its 2D and 3D structure.

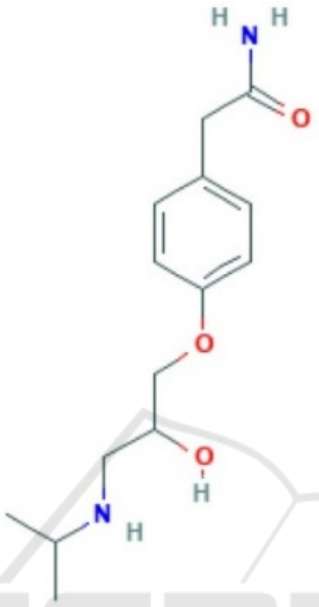

Figure 3: Atenolol 2D structure (https://pubchem.ncbi.nlm.nih.gov/compound/Atenolol)

Figure 4: Atenolol 3D structure (https://pubchem.ncbi.nlm.nih.gov/compound/Atenolol).

It's a white crystalline powder worn at a melting point around 158-160°C. It is also slightly soluble in water. At 25°C, only 13.3g of Atenolol can be mixed up with one litre of water. It has a molarity of 0.05M. It is also a monocarboxylic acid. It has a $pKa = 9.6$ (https://pubchem.ncbi.nlm.nih.gov/compound/Atenolol). Table 3 is a graph that shows other properties of Atenolol.

Table 3: Atenolol chemical and physical properties (https://pubchem.ncbi.nlm.nih.gov/compound/Atenolol).

Property Name	**Property Value**	**Reference**
Molecular Weight	266.34	Computed by PubChem 2.1 (PubChem release 2021.05.07)
XLogP3	0.2	Computed by XLogP3 3.0 (PubChem release 2021.05.07)
Hydrogen Bond Donor Count	3	Computed by Cactvs 3.4.8.18 (PubChem release 2021.05.07)
Hydrogen Bond Acceptor Count	4	Computed by Cactvs 3.4.8.18 (PubChem release 2021.05.07)
Rotatable Bond Count	8	Computed by Cactvs 3.4.8.18 (PubChem release 2021.05.07)
Exact Mass	266.16304257	Computed by PubChem 2.1 (PubChem release 2021.05.07)
Monoisotopic Mass	266.16304257	Computed by PubChem 2.1 (PubChem release 2021.05.07)
Topological Polar Surface Area	84.6 Å²	Computed by Cactvs 3.4.8.18 (PubChem release 2021.05.07)
Heavy Atom Count	19	Computed by PubChem
Formal Charge	0	Computed by PubChem
Complexity	263	Computed by Cactvs 3.4.8.18 (PubChem release 2021.05.07)
Isotope Atom Count	0	Computed by PubChem
Defined Atom Stereocenter Count	0	Computed by PubChem
Undefined Atom Stereocenter Count	1	Computed by PubChem
Defined Bond Stereocenter Count	0	Computed by PubChem
Undefined Bond Stereocenter Count	0	Computed by PubChem
Covalently-Bonded Unit Count	1	Computed by PubChem
Compound Is Canonicalized	Yes	Computed by PubChem (release 2021.05.07)

3.2 Drug Pharmacology

If a doctor has prescribed Enalapril, the patient must be affected by Hypertension, heart failure, or heart attack.

Enalapril works as an ACE(Angiotensin-converting-enzyme) inhibitor; it belongs to the ACE inhibitor drug class. It works by inhibiting the mechanisms the body customarily used to maintain blood pressure. Angiotensin 1 is officially called angiotensin. It's an enzyme that is contained in a human's bloodstream. Its chemical formula is C62H89N17O14 (https://pubchem.ncbi.nlm.nih.gov/compound/Angiotensin-I). Figure 8 shows it's structure. It is formed by an enzyme called "renin" produced by the kidney on a protein called "angiotensinogen" produced by the liver. It has no direct biological activity. It just exists as a precursor of angiotensin 2.

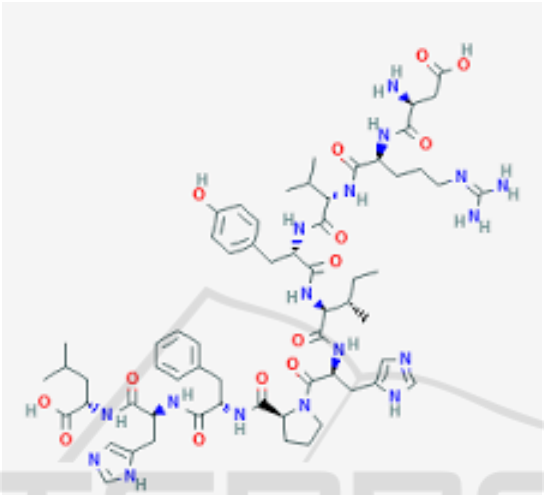

Figure 5: Structure of Angiotensin 1 (https://pubchem.ncbi.nlm.nih.gov/compound/Angiotensin-I).

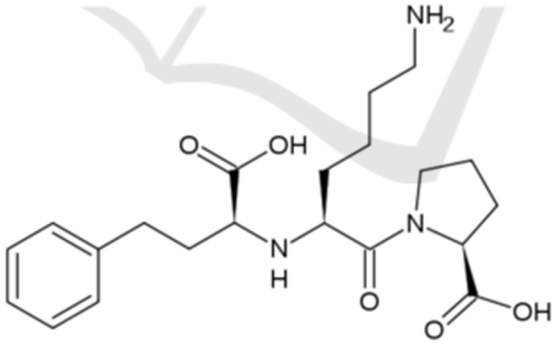

Figure 6: Structure of Angiotensin converting enzyme (Proteopedia. 2021).

ACE (Angiotensin-converting enzyme) is an enzyme that converts Angiotensin 1 to Angiotensin 2. The Figure 9 shows how its structure looks.

Angiotensin 2 is an enzyme that narrows our blood vessels and releases hormones to increase our blood pressure. It has a chemical formula C50H71N13O12. Figure 10 shows its structure.

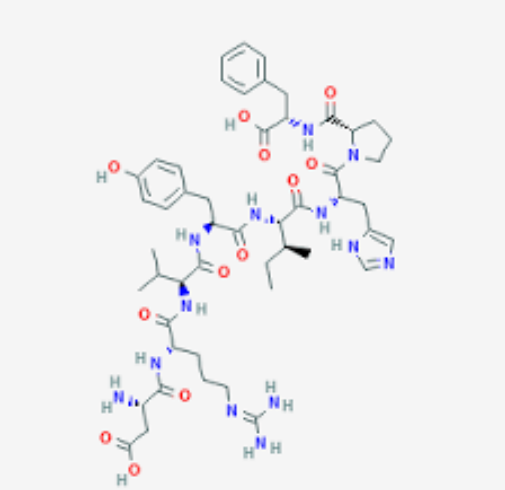

Figure 7: Angiotensin 2 structure (https://pubchem.ncbi.nlm.nih.gov/compound/Angiotensin-II).

Enalapril (ACE inhibitor) stops this conversion to reduce the Angiotensin two in our body. Usually, Angiotensin-Converting Enzyme will cut Angiotensin 1 as a protease (an enzyme that cuts other peptides) and form Angiotensin 2. What Enalapril does is bind with Angiotensin-Converting Enzyme before it binds with Angiotensin 1. That makes it can't attach to Angiotensin 1 anymore. Like if a boy (ACE) wanna eat an apple (Angiotensin 1), but someone has put a baseball (Enalapril) in his mouth. So he can't eat the apple (Angiotensin 1) anymore, it means there is no Angiotensin 2 produced anymore. Therefore, it can reduce our blood pressure to the average level. This means that more salt is going to pass through our kidneys in an aqueous solution.

At last, it will be mixed into our urine for us to pee it out. With the reduction of fluid in our body, there is going to be a smaller volume of blood for our hearts to pump. All in all, by relaxing our blood vessels and reducing the amount of fluid in them, strain for the heart is also decreasing. That's the reason why Enalapril can be used in other two types of cardiovascular disease rather than only blood pressure.

Figure 8: A photo of Enalapril drug box (Prescriptiongiant. 2021).

Enalapril is always an oral tablet. Figure 11 shows how is a Enalapril drug box looks like. It's typically taken once or twice a day. Doctors may suggest taking it before bed because it will make you dizzy.

The main reason doctors prescribed you Atenolol probably you may have Hypertension, abnormal rhythms, angina, heart failure or heart attack.

People heart pumps blood to their body through a network of blood vessels, known as the circulatory system. Then it supplies the cells in the body with the oxygen and nutrient they need. Atenolol works as a beta-blocker by blocking hormones. There is a group of substances released in blood in responses to physical and emotional stress. Adrenaline and Noradrenaline.

Adrenaline, chemical structure shows in Figure 12, is a chemical produced by people's body and released during increased stress or sudden vigorous

activity. It has many uses in bodies. For example, It can improve the strength of the heart; therefore, it can deliver more blood to the muscles. It can also open the airways of the lungs, which increases the oxygen level in human's blood.

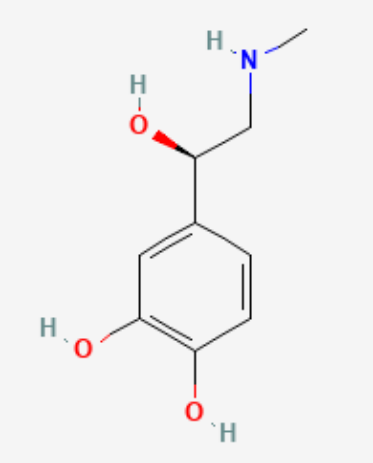

Figure 9: Adrenaline structure (https://pubchem.ncbi.nlm.nih.gov/compound/Epinephrine).

Noradrenaline, shows is a neurotransmitter in both the peripheral and central nervous systems. Its structure is showed in Figure 13. It also produces many effects on the body. The most notable is the "flight or fight" response to perceived danger.

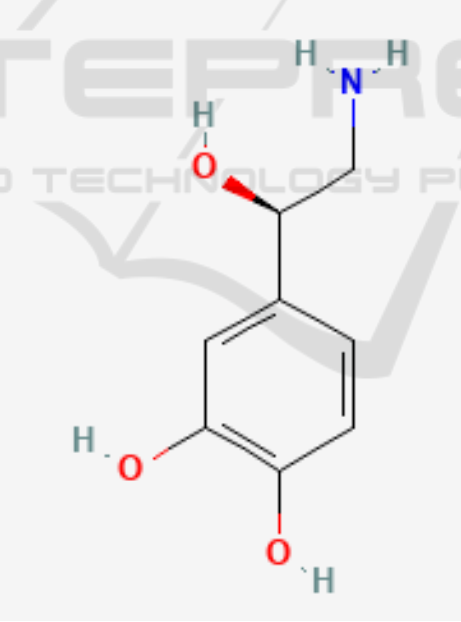

Figure 10: Noradrenaline structure (https://pubchem.ncbi.nlm.nih.gov/compound/Norepinephrine).

Like many other cell types, cardiac myocytes possess membrane receptors that respond to Noradrenaline and adrenaline, called adrenoceptors. It makes up a vital part of the sympathetic nervous system. There are two significant categories of adrenoceptor, which is alpha and beta. There are different subtypes for each of them. These vary in their structure-function, ligand specificity, and location of expression within the body. As for the heart itself, the primary adrenoceptor is the beta one receptor.

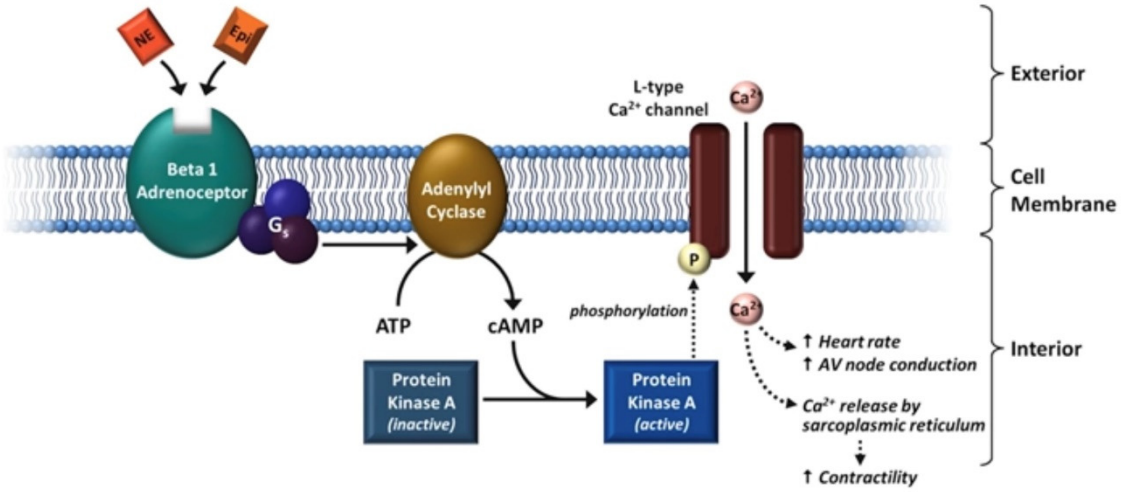

Figure 11: Mechanism of Atenolol works in human's body (Strong Medicine. 2017).

In Figure 15, there is a cardiac myocyte with a beta 11 adrenoceptor sitting there. It is couple to something called g-protein, a family of proteins that switch molecules inside cells and are involved in transmitting signals from various stimuli outside the cell to the inside of the cell. As the figure shows, there are three different subunits. Beta 1 adrenoceptor can respond to either adrenaline or Noradrenaline. With binding to either adrenaline or Noradrenaline, one of the subunits of g-protein will be released. This increased the Adenylyl cyclase activity, which converts ATP (Adenosine triphosphate) to cyclic AMP, a second messenger important in many biological processes (Alberts, 2008). cAMP, in turn, activates protein kinase A, then kinase A phosphorylates a subtype of the calcium channel called the "l-type" calcium channel. It increases the calcium entry into the cell cytosol. As a result, it increases the heart rate and cardiac contractility.

To this point, what beta-blocker does is quite apparent. It decreases the heart rate and cardiac contractility by blocking beta one adrenoceptor bind to adrenaline or Noradrenaline.

Figure 12: Atenolol drug box (Christine Whitehead / Alamy Stock Photo. 2018).

Atenolol is both oral and intravenous. To treat different types of cardiovascular diseases, there are different kinds of ways to use them. Figure 16 shows how's Atenolol drug box looks like.

Always follow what doctors said before using it.

3.3 Drugs Economics

Enalapril is an inexpensive drug. It can be used alone, or with other drugs. It is less popular than the similar drug. It is available in branded and regular versions.

It is usually covered by health insurance, but some drug coupons or cash prices may be lower. GoodRx's most common version of Enalapril starts at about $12.00, 69% off its average retail price of $39.14 (GoodRx contributors. (2011-2021) Enalapril. https://www.goodrx.com/enalapril).

Atenolol is also an inexpensive drug used to treat high blood pressure and to prevent chest pain. It is also used to protect the heart during a heart attack. It's slightly more popular than its peers. It comes in generic and branded versions. Same as Enalapril, it is also covered by health insurance and cheaper in some drug coupons and cash prices. The most common version of Atenolol, GoodRx, starts at about $1.77, 84% off the average retail price of $11.12 (GoodRx contributors. (2011-2021) Atenolol. https://www.goodrx.com/atenolol).

4 DISCUSSIONS

From the Drug pharmacology, how Enalapril works are logical. But what makes it less popular than similar drugs? Side effects are noteworthy.

Enalapril is the best option for facing stroke volume, increased ejection fraction, and decreased mean arterial pressure. But it was associated with the highest incidence of cough, gastrointestinal discomfort, and more significant deterioration in renal function. By giving interventions and comparisons to patients with chronic kidney diseases and patients with chronic heart failure, they have found that Trandolapril would be the best choice to reduce diastolic and systolic blood pressure. Ramipril was associated with the lowest incidence of all-cause mortality. Lisinopril had the lowest efficiency on lowering the diastolic and systolic blood pressure, and was associated with the highest incidence of all-cause mortality (Zhang, Dong, Sun, Zhang, Chen, Ma, 2011).

Compare to Enalapril, Atenolol would be a better choice for Hypertension. Atenolol was given to 20 patients in M M Ibrahim et al, 1981. Six of them had cardiomegaly with recent exertional dyspnea, three had accelerated Hypertension, and three were diabetics. They were asking to take Atenolol once a day (100-300 mg) for two weeks. It controlled both standing blood pressure and the supine. Within two weeks treatment, a significant hypotensive action has developed. Even after a sudden interruption of therapy, control of Hypertension was still maintained for two weeks. No patient had postural or postexercise hypotension. The drug appeared to exert its maximum hypotensive effect at the 100-mg dosage. Except for the impairment of glucose tolerance in diabetic patients, Atenolol had minimal side effects (M M Ibrahim, 1981).

By comparing with the different mechanisms of action of both drugs. It's not hard to find that even they have two completely different mechanisms, what both of them are doing is inhibiting some mechanisms used to act in human bodies to make blood pressure to an average level. And one thing that is valuable for mentioning is they both belong to their drug classes. (Beta-blockers drug class and ACE inhibitors drug class) With this means, other drugs used in Hypertension follow the same ideas. Not only beta-blockers drug class

5 CONCLUSIONS

In summary, medicine is not as arcane as people used to think. It's just something that can affect original out-controlled mechanisms in the human body and is used to make people's various physical indicators to a healthy level. So that people can keep healthy. The side effect is a significant factor for doctors to be concerned about whether prescribed a type of medicine or not. Whether a drug is successful or not, it is concerned with how well the medicine treats the diseases and its few side effects. These two ideas help discover new drugs with high popularity a lot.

REFERENCES

American Society of Health-System Pharmacists 2017; Drug Information 2017. Bethesda, MD. 2017, p. 2091

Alberts et al. (2008). "Molecular Biology of the Cell" (4th edition); page 855

Christine Whitehead / Alamy Stock Photo. (2018) Atenolol Hypertension medication. https://www.alamy.com/stock-photo-atenolol-hypertension-medication-172962896.html?pv=1&stamp=2&imageid=41312320-D0C3-48C0-A9F6-CBF5DD339949&p=50841&n=0&orientation=0&pn=1&searchtype=0&IsFromSearch=1&srch=foo%3dbar%26st%3d0%26pn%3d1%26ps%3d100%26sortby%3d2%26resultview%3dsortbyPopular%26npgs%3d0%26qt%3datenolol%26qt_raw%3datenolol%26lic%3d3%26mr%3d0%26pr%3d0%26ot%3d0%26creative%3d%26ag%3d0%26hc%3d0%26pc%3d%26blackwhite%3d%26cutout%3d%26tbar%3d1%26et%3d0x00000000000000000000%26vp%3d0%26loc%3d0%26imgt%3d0%26dtfr%3d%26dtto%3d%26size%3d0xFF%26archive%3d1%26groupid%3d%26pseudoid%3d%26a%3d%26cdid%3d%26cdsrt%3d%26name%3d%26qn%3d%26apalib%3d%26apalic%3d%26lightbox%3d%

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Drug Bank. (2021) Atenolol. https://go.drugbank.com/drugs/DB00335

GoodRx contributors. (2011-2021) Enalapril. https://www.goodrx.com/enalapril

GoodRx contributors. (2011-2021) Atenolol. https://www.goodrx.com/atenolol

Loftsson T et al; Acta Ophthalmologica 88(3): 337-41 (2010). Available from, as of Oct 27, 2017: https://onlinelibrary.wiley.com/doi/10.1111/j.1755-3768.2008.01495.x/pdf

M M Ibrahim and R Mossallam, Ibrahim, M. M., M M Ibrahim Search for more papers by this author, Mossallam, R., & R Mossallam Search for more papers by this author. (1981, August 1). Clinical evaluation of atenolol in hypertensive patients. Circulation. http://circ.ahajournals.org/content/64/2/368

National Center for Biotechnology Information (2021). PubChem Compound Summary for CID 5388962, Enalapril. https://pubchem.ncbi.nlm.nih.gov/compound/Enalapril

National Center for Biotechnology Information (2021). PubChem Compound Summary for CID 2249, Atenolol. https://pubchem.ncbi.nlm.nih.gov/compound/Atenolol

National Center for Biotechnology Information (2021). PubChem Compound Summary for CID 3081372, Angiotensin I. https://pubchem.ncbi.nlm.nih.gov/compound/Angiotensin-I

National Center for Biotechnology Information (2021). PubChem Compound Summary for CID 172198, Angiotensin II. https://pubchem.ncbi.nlm.nih.gov/compound/Angiotensin-II

National Center for Biotechnology Information (2021). PubChem Compound Summary for CID 5816, Epinephrine. Retrieved August 31, 2021 from https://pubchem.ncbi.nlm.nih.gov/compound/Epinephrine.

National Center for Biotechnology Information (2021). PubChem Compound Summary for CID 439260, Norepinephrine. Retrieved August 31, 2021 from https://pubchem.ncbi.nlm.nih.gov/compound/Norepinephrine.

Proteopedia. (2021) Angiotensin-Converting Enzyme https://proteopedia.org/wiki/index.php/Angiotensin-Converting_Enzyme

Prescriptiongiant. (2021) Enalapril. https://prescriptiongiant.com/product/enalapril/

Strong Medicine. (2017) Antiarrhythmics (Lesson 3 – Beta Blockers). https://www.google.ca/url?sa=i&url=https%3A%2F%2Fm.youtube.com%2Fwatch%3Fv%3DpK97Ni0fGJ8&psig=AOvVaw3srbGieGoAwLdHPFWIUfiC&ust=1629737788539000&source=images&cd=vfe&ved=2ahUKEwiQwvzAjMXyAhVlrHIEHTaQAscQr4kDegUIARDBAQ

U.S. National Library of Medicine. (2021) High Blood Pressure. https://medlineplus.gov/highbloodpressure.html

World Health Organization. (n.d.). Hypertension. World Health Organization. https://www.who.int/china/health-topics/hypertension

World Health Organization. (n.d.). Hypertension. World Health Organization. https://www.who.int/news-room/fact-sheets/detail/hypertension

Zhang P, Dong G, Sun B, Zhang L, Chen X, Ma N, et al. (2011) Long-Term Exposure to Ambient Air Pollution and Mortality Due to Cardiovascular Disease and Cerebrovascular Disease in Shenyang, China. PLoS ONE 6(6): e20827. https://doi.org/10.1371/journal.pone.0020827