Cross Examination of Atenolol and Canderstan Cilexetil on the Treatment of Hypertension

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Keywords: Hypertension (HTN), Atenolol, Canderstan Cilexetil/Canderstan, Beta-1 Adrenergic Receptor, Angiotensin II Receptor (Type-1).

Abstract: Hypertension is a serious medical condition that has led to approximately a total of 7.6 million deaths annually throughout the globe. In retrospect of the entire medical history, many drugs had been used for the treatment of hypertension, but none had presented a consummate solution that could eradicate or prevent hypertension previously at all. Nowadays, with the fast-developing medical industries, people can gain access to more medications targeting hypertension with a far wider range of scope and through more convenient facilitations. Drugs such as atenolol and canderstan cilexetil had furthermore also became some of the most popular drugs used to treat high blood pressure with the precondition of a prospering modern medical market. In order to resolve one of the most difficult medical problems that hovered through the entire human history until now, it is essentially necessary to understand what is the best equipment that can defeat the abhorrent enemy in the entire medical field----hypertension.

1 INTRODUCTION

Hypertension (HTN), commonly known as high blood pressure (HBP) by the public, is often considered as one of the most dreadful causes of cardiovascular dysfunction as it induces to approximately 54% of all stroke diagnoses and 47% of all coronary heart diseases discovered world-widely (J;, A. H. B. F. C, 2011). As the culprit contributing to a total of 7.6 million deaths annually throughout the globe, HTN has the highest mortality rate in comparison to any other risk factors for cardiovascular diseases or kidney failures (J;, A. H. B. F. C, 2011). Overall, 80% of diagnoses for HTN were found in low- and middle-income countries (J;, A. H. B. F. C, 2011), making it a great struggle related to poverty and population aging also since the population of age 69 and older would have the possibility to be diagnosed with HTN with a 50% chance, much higher in comparison to a 38% for the younger age group (GL;, O. R. V. B. (n.d.). As partially shown in *Table 1*, in China, an average of 23.2% of the adult population during 2012-2015 was diagnosed with HTN, while another 41.3% of the entire Chinese adult group were discovered to have symptoms indicating pre-HTN, demonstrating a high prevalence for HTN in China and throughout the globe (Wang, 2018).

Table 1: Trend of hypertension prevalence in Chinese adults from year 2007-2015 [3-4].

Years	2007	2009	2010	2011	2013	2015
Prevalence (%) of HTN in Chinese adult population	26.6	29.6	33.5	22.8	24.5	37.2

According to *the American College of Cardiology/American Heart Association Guideline for the Prevention, Detection, Evaluation, and the Management of High Blood Pressure in Adults*, systolic HTN is confirmed once one's blood pressure has reached 130 mm Hg or higher, while diastolic HTN would be confirmed once the patient's blood level has reached 80 mm Hg or higher (Whelton, 2017). Patients diagnosed with HTN were often found to be accompanied by symptoms including extensive nose bleeding, dizziness, or shortness of breath when their blood pressure has reached a high life-threatening stage while demonstrating minor or no symptoms during normal-day activities (Mayo

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Foundation for Medical Education and Research, 2021). Although the essential etiology about a single trigger causing HTN still remains to be unclear, a lack of strong blood circulation, weakening of blood vessel contraction, and an excessive force damaging the internal structures of the blood vascular system could all be the calmative causes for HTN accompanied by external conditions especially related to old age or bad physical circumstances (diet, environment, etc.) (Mayo Foundation for Medical Education and Research, 2021).

Drugs such as Atenolol and Canderstan Cilexetil acting as essential blockers had been commonly used to treat HTN throughout the history of modern medicine due to their dominance in the market. Atenolol, a Beta-1 cardio-selective adreno-receptor blocker (Mayo Foundation for Medical Education and Research, 2021), was originally developed by the Imperial Chemical Industries (ICI) in 1976 and has been approved by the public in 1981 in America due to its effectiveness and safety as an anti-hypertensive drug in its previous clinical trials (https://en.citizendium.org/wiki/National_Library_of_Medicine.). Canderstan Cilexetil, an angiotensin-receptor blocking agent treating HTN, registered by its brand name as Atacand in the public, was developed by the corporation Takeda in the Medical field on the other hand with a more different mechanism than Atenolol on a pharmaceutical scale (Candesartan Cilexetil). Overall, these two drugs had all demonstrated their efficiency in treating HTN.

In this literature review, these two most dominant drugs in the medical market, atenolol and canderstan cilexetil, will be cross-examined based on their chemical properties, mechanism of action, and modes of delivery from both a therapeutical and economic standpoint in order to search for the most optimal solution on the treatment of hypertension.

2 DESCRIPTION OF CHEMICAL STRUCTURES OF DRUGS

2.1 Atenolol (Generic Name)

Atenolol, commonly recognized by its brand name as Tenoretic or Tenormin (https://pubchem.ncbi.nlm.nih.gov/compound/atenolol), has a molar mass of 266.336 g·mol−1 and is solid in the form as white crystalline powder under room temperature (Libretexts, 2020); (https://www.chem960.com/cas/29122687/). As shown in *Figure 1*, Atenolol has a chemical composition of C14H22N2O3 (https://pubchem.ncbi.nlm.nih.gov/#query=C14H22N2O3), and its IUPAC name is 2-(4-{2-hydroxy-3-[(propan-2-yl) amino] propoxy} phenyl) acetamide (https://pubchem.ncbi.nlm.nih.gov/compound/Angiotensin-II#section=Biologic-Description). On the behalf of its chemical properties, Atenolol has an approximate melting point ranging from 146-148°C along with a pka value of 9.6 in its internal structure (https://go.drugbank.com/drugs/DB00335); (Karaman, 2016). As a chemical substance that is highly soluble in liquid including methanol and hydrochloric acid, Atenolol also possesses a solubility of 13300 mg/L at the temperature of 25°C (https://pubchem.ncbi.nlm.nih.gov/compound/atenolol#section=Solubility).

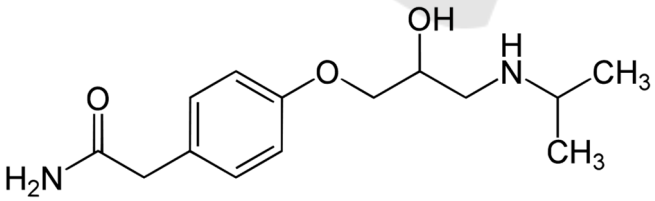

Figure 1: Chemical structure of Atenolol.

2.2 Canderstan Cilexetil (Generic Name)

Canderstan Cilexetil, registered as Atacand as its public brand name, has a common molar mass of 440.463 g·mol−1 in normal state (https://pubchem.ncbi.nlm.nih.gov/compound/Candesartan-cilexetil). As shown in *Figure 2*, Canderstan Cilexetil has a chemical structure written as C33H34N6O6 and was named in the form of IUPAC nomenclature as 1-{[(cyclohexyloxy) carbonyl]oxy}ethyl2-ethoxy-1-{[2'-(1H-1,2,3,4-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl]methyl}-1H-1,3-benzodiazole-7-carboxylate (Candesartan Cilexetil, 2021). Canderstan also has a strong acidic pka value of 4.23 and a strong basic pka value of 1.45 (https://chemaxon.com/products/calculators-and-predictors#pka.), along with a water solubility value

at 0.00204mg/ml under normal condition (http://www.vcclab.org/lab/alogps/); (https://pubmed.ncbi.nlm.nih.gov/11749573/.). Canderstan Cilexetil has a single chiral center at its cyclohexyloxycarbonyloxy ethyl ester group, indicating its specific characteristics as a chemical compound acting as an angiotensin-receptor blocking agent (Pharmaceuticals, A. N. I., 2020). Functions of its chemical structure on the behalf of treating hypertension will be discussed furthermore in the next section.

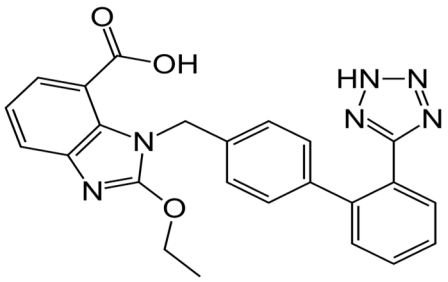

Figure 2: Chemical structure of Canderstan Cilexetil.

3 DISCUSSION OF DRUG PHARMACOLOGY

3.1 Drug Targets Description and Characteristics

(1) β-1 Adrenergic receptor & its corresponding hormones

The Beta-1 receptor is a specific adrenergic receptor primarily found within the body's heart and kidney cells (CV;, A. S. P. (n.d.). As a receptor responsible for the transportation of signals within the sympathetic nervous system, the Beta-1 adrenergic receptor majorly passes signals through the Gs alpha subunit that triggers the initiation of a cAMP-dependent pathway and eventually amplifies the Beta-1 receptor's functions within the body (CV;, A. S. P. (n.d.). With the activation of beta-1 receptors through the cAMP-dependent pathway, the beta-1 receptors inside the heart can thus perform their tasks as receptors responsible of increasing the contractions within the ventricular muscle, sinoatrial node, and the atrioventricular node that amplify heart rate and blood pressure in combination (CV;, A. S. P. (n.d.); (Steinberg SF). Based on its characteristics to make use of the Gs alpha subunit as passageway, the structure of Beta-1 receptor is specifically classified as G protein-coupled receptor (GPCRs) that has seven transmembrane regions with two different terminal (N-terminus & C-terminus) located both on the outside and inside of the cell (M.T., P. (n.d.).

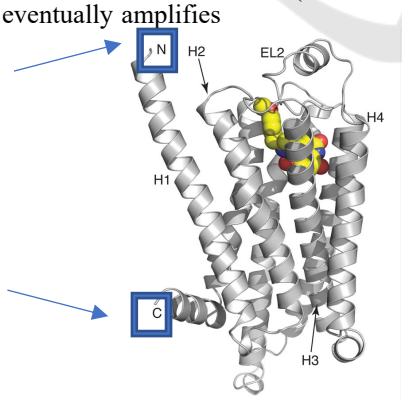

Figure 3: Structure of the β-1 adrenergic receptor (https://www.esrf.fr/news/spotlight/spotlight145/index_html).

Description of Figure:

Figure 4 has demonstrated the typical structure of the Beta-1 receptor (as GPCR) located in heart cells with labels of its structure: (extracellular N-terminus & intracellular C-terminus). These receptors often have the characteristics to be extremely dynamic and easily conformational between its active state and inactive state. These characteristics all eventually

contributes to Beta-1 receptor's extreme instability on the performance of its job as a blood pressure regulator and can easily be disruptive and has high potential to trigger HTN (https://www.esrf.fr/news/spotlight/spotlight145/index_html.). (End of figure description)

A variety of hormones including dopamine, epinephrine, and norepinephrine can bind to the Beta-1 receptors within the heart, kidney, and sympathetic nervous system. While dopamine and norepinephrine have the affinity to target both Beta-1 and Beta-2 receptor almost equally, the hormone epinephrine has demonstrated the strongest affinity toward the binding to Beta-1 receptor, making it the most effective hormone in the Beta-1 pathway to affect blood pressure and muscle contraction amongst all the other hormones triggering the activation of beta-1 receptor (Lennarz, 2013).

(2) Angiotensin II (Ang II) & Type 1 (AT1) Angiotensin II receptor

Angiotensin II (Ang II) is an organic peptide hormone derived from Angiotensin I in the renin-angiotensin system (RAAS) that can raise blood pressure through causing contraction within blood vessels and increasing sodium concentration within the kidney (I;, F. F. M. K. T. (n.d.). Thus, once too much Ang II has accumulated within human organs or in the RAAS system, it could potentially lead to serious problems that would trigger HTN. Inside the cardiovascular vessels, Ang II acts as one of the main factors having a significant effect in the renin-angiotensin system that regulates the cardiovascular metabolism and homeostasis through the pathway of its type 1 (AT1) and type 2 (AT2) receptors (I;, F. F. M. K. T. (n.d.).

The human AT1 Ang II receptor is specifically encoded between the 29th to 10th position within the protein sequence P30556, which has the conserved feature of TM helix 1 that is classified to have a seven-transmembrane helix domain (https://www.ncbi.nlm.nih.gov/Structure/cdd/cd15192.); (CDD Conserved Protein Domain Family: 7tmA_AT1R (nih.gov) (database)). Based on this domain's specific function, the AT1 receptor therefore can perform blood cell proliferation easily due to its highly transmembrane feature (to pass essential particles across cellular membrane) which eventually contributes to the increase in blood pressure with the multiplication of blood cells (CDD Conserved Protein Domain Family: 7tmA_AT1R (nih.gov) (database). Thus, the activation of the AT1 receptor domain through Ang II has become one of the most evident features contributing to HTN on a molecular scale.

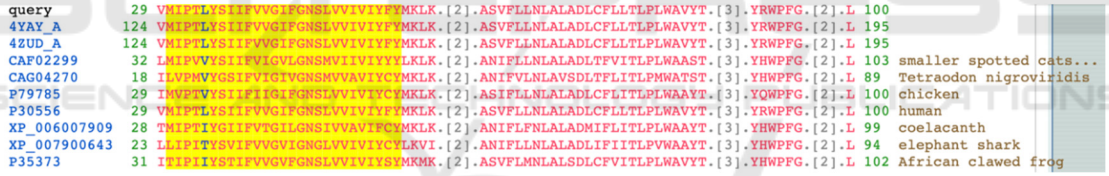

Figure 4 Protein Sequences of AT1 Ang II receptor in various animals (CDD Conserved Protein Domain Family: 7tmA_AT1R (nih.gov) (database).

Description of Figure:

Figure 5 has demonstrated a variety of protein sequences encoding the AT1 receptor in RAAS system responsible of receiving Ang II peptide (CDD Conserved Protein Domain Family: 7tmA_AT1R (nih.gov) (database). The query sequence P30556 represents for the protein sequence in human that coded for the specific structure of AT1 receptor, while the highlighted yellow regions in all these sequences represent the feature TM helix 1 in the AT1 receptor coding sequence (CDD Conserved Protein Domain Family: 7tmA_AT1R (nih.gov) (database). (End of figure description)

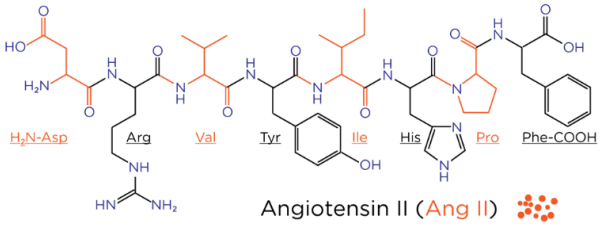

Figure 5 Chemical structure of Angiotensin II (CDD Conserved Protein Domain Family: 7tmA_AT1R (nih.gov) (database).

3.2 Drug Effect on Targets Description

(1) Atenolol on β-1 Adrenergic receptor

Atenolol, a beta-1 selective agent, has been widely used as an antihypertensive drug that specifically targets the Beta-1 receptor to lower blood pressure through competing with other hormones for the binding site (extracellular N-terminus) on the receptor (Hasanah, Dwi Utari, Pratiwi, 2019). Through connecting its methyl group onto the extracellular N-terminus of the beta-1 receptors located in the myocardial regions, atenolol thus inhibits their action to increase blood pressure and cardio muscular contraction through producing inotropic and negative chronotropic activities (Hasanah, Dwi Utari, Pratiwi, 2019); (https://pubchem.ncbi.nlm.nih.gov/source/hsdb/6526#section=Mechanism-of-Action-(Complete)). The negative chronotropic activities initiated by atenolol within heart tissues such as the sinoatrial node would eventually decrease the rate of electrical signal discharges from the sinoatrial node and gradually lowers heart rate by approximately 25-35% (https://pubchem.ncbi.nlm.nih.gov/source/hsdb/6526#section=Mechanism-of-Action-(Complete)). Atenolol would also reduce the regular cardiac output by about 20% through its binding with the Beta-1 receptor on a secondary position in comparison to the decrease of heart rate and myocardial muscular contraction (https://pubchem.ncbi.nlm.nih.gov/source/hsdb/6526#section=Mechanism-of-Action-(Complete)). Although atenolol trigger could possibly influence the increase in oxygen requirements through stimulating left ventricular fiber length to amplify end-diastolic pressure especially in patients diagnosed with cardiac failure, it generally would reduce oxygen consumption through decreasing myocardial contraction and eventually lead to pain-relief of muscles in the myocardial region particularly effective for patients diagnosed with HTN-related angina pectoris (https://pubchem.ncbi.nlm.nih.gov/source/hsdb/6526#section=Mechanism-of-Action-(Complete)).

A high dosage of the atenolol drug might possibly lead to sinus arrest within patients in a life-threatening stage. Moreover, atenolol could also lead to increase in patient's stroke index by about 10% as one of its side-effects (https://pubchem.ncbi.nlm.nih.gov/source/hsdb/6526#section=Mechanism-of-Action-(Complete)).

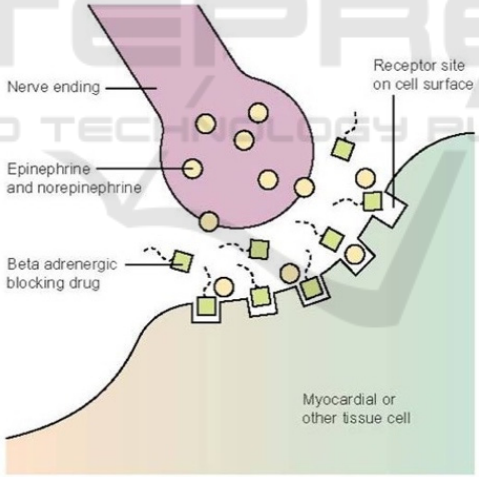

Figure 6: Mechanism of Beta-adrenergic blocking drug (atenolol) binding to receptor site (http://dxline.info/diseases/beta-blocker).

Description of Figure:

Figure 7 has demonstrated a simple illustration for the process of atenolol competition with other naturally occurring hormones for the binding site of Beta-1 receptor on myocardial tissue cells. The atenolol chemicals would reach the receptor site on cell surface before hormones such as epinephrine or norepinephrine in the sympathetic nervous system to alter the receptor's function with a high affinity (http://dxline.info/diseases/beta-blocker.). (End of figure description)

(2) Canderstan Cilexetil on Type 1 (AT1) Angiotensin II receptor

Canderstan Cilexetil has been commonly used as an angiotensin-receptor blocker (ARB) medicine for treating hypertension and many of its related complications. Canderstan cilexetil, once rapidly converted into its complete form as Canderstan

inside the body (see next section for further details/reasons), will actively seek for AT1 Ang II receptors and attaches itself onto the target. Once Canderstan is attached to AT1 receptors, it will restrain Ang II to connect to these receptors and thus stops Ang II stimulating the AT1 receptors to produce aldosterone that could lead to vasoconstriction through reabsorbing water and sodium which could eventually lead to HTN if the pressure exerted by this action (vasoconstriction) is too high (https://go.drugbank.com/drugs/DB11842).

In the whole process, as shown in *Figure 8*, Canderstan cilexetil acts as an antagonist toward the renin-angiotensin-aldosterone (RAAS) system that would selectively competes for binding site with Ang II and blocks the aldosterone secreting effects and vasoconstrictor of Ang II in many parts of the human body including the adrenal gland and vascular smooth muscle (Giacchetti G; Opocher G; Sarzani R; Rappelli A; Mantero F; (n.d.)). On a closer look, the adrenal gland discussed in this process would directly trigger the production of epinephrine within itself that could furthermore initiates the binding process to the beta-1 adrenergic receptor and raises blood pressure if nothing acts to stop the reaction (Adrenal glands. Johns Hopkins Medicine. (n.d.)). Thus, Canderstan cilexetil's blockade onto the Ang II receptor would actually not only help stopping blood pressure to be raised through processes within the RAAS system, but it would also help to stop epinephrine from binding onto the beta-1 receptor in advance since once AT1 receptors in the adrenal gland are inactivated, the adrenal gland would also stop to produce the corresponding chemicals required in the body. This process furthermore proves this drug's high efficiency in stopping HTN since canderstan could has an effect in both systems discussed (beta-1 adrenergic & Angiotensin II receptor) in this specific paper.

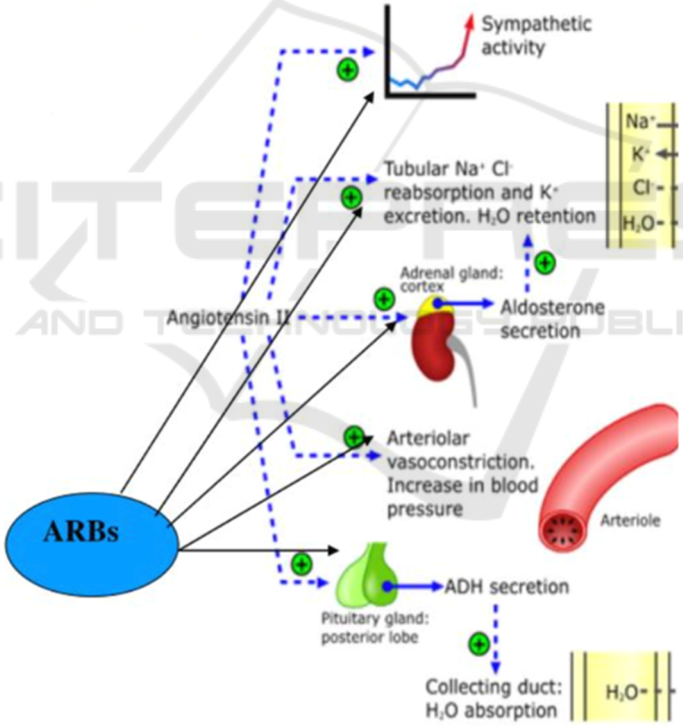

Figure 7: Mechanism of angiotensin receptor blocking drug (canderstan) binding to receptor (Aquarius, 2013).

3.3 Modes of Delivery and Related Characteristics

(1) Atenolol

The most traditional way of absorbing atenolol for treating hypertension is most directly related to oral delivery. It is suggested that for an average adult diagnosed with hypertension, atenolol should be taken on an average day with 50-100mg three times per day for a month's period (Choudhary, 2016).

Although constantly delivered to patients orally, the bioavailability of absorbing atenolol through this mode of delivery has actually been proven to be very low with only an index of 50% which directly infers that it would take almost 2 weeks for atenolol to actually make an effect within the human body after

taking it orally. Recently, studies had shown that the process of transdermal delivery could actually be a potential alternative to oral absorption since many clinical studies has all demonstrated that transdermal delivery of atenolol could actually increase the therapeutic efficacy for atenolol to be dissolved in the body. Since atenolol has a relatively high pka value of 9.6 under normal circumstances, the dissolution of atenolol within body through transdermal iontophoresis could possibly be a better solution than delivering atenolol to patients through the mouth. Essentially, iontophoresis could reduce the lag time of medical effect to happen, increase rate of transportation of atenolol within the body, and allow better control over the delivery of drugs (Ramkanth, 2018); (SM;, M.-D. S. N.-J. M. R. G. (n.d.).

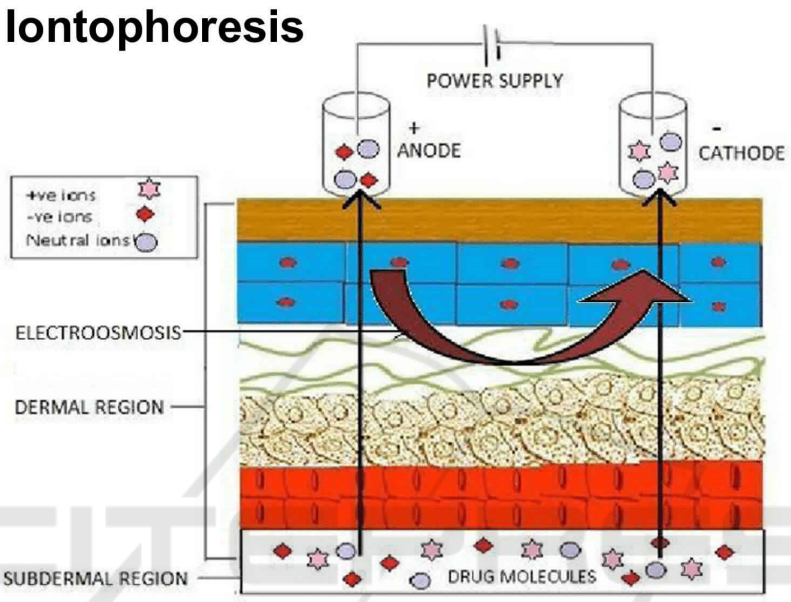

Figure 8: Illustration of Transdermal Iontophoresis (Team, H. J., & Team, H. J. (2018).

Description of Figure:

Figure 9 has demonstrated a typical illustration of the mechanism for iontophoresis on the skin surface. On the surface, a simple battery powered direct current (DC) has been connected with both the anode (+ charge) and cathode (- charge) to transport drug chemicals or macromolecules through the three layers of the skin into the blood vessels and inner part of the body through facilitating ions both charged positively and negatively in the electrical current. The transportation pathway of the drug particles directly forms a loophole with the electrical power supply in this way, giving drugs a faster rate to be transported with electrical charges (Team, H. J., & Team, H. J. (2018). (End of figure description)

(2) Canderstan Cilexetil

Before absorbed by patients, canderstan cilexetil is only a biological inactive compound (prodrug) that still requires to be converted into its complete form in order to make an impact to the targeted receptors within the body. Once orally delivered, canderstan cilexetil will directly enters the gastrointestinal tract and become bioactivated through ester hydrolysis, which will eventually convert canderstan cilexetil into canderstan---the full selective AT1 receptor antagonist/blocker. It is said that canderstan could only be poorly absorbed after delivered to the patient orally in its complete form, thus the ester prodrug form of canderstan cilexetil must be prepared in order to exert the maximum effect to the body as an organic drug. After canderstan performs its function inside the body, the drug chemical will mainly be excreted unchanged outside the body via urine and feces. The drug chemical would undergo minor hepatic metabolism into the inactivate metabolite and thus transport outside body in an approximate time of 9 hours (roughly the half-life for canderstan). It is suggested that canderstan cilexetil should be taken orally per time for a monthly prescription time with up to a 32 mg since 64% of the canderstan cilexetil would be excreted outside the body during absorption the form of feces, so a relatively large amount of the prodrug is required to be taken in (Khawaja, 2011).

4 DISCUSSION OF DRUG ECONOMICS

4.1 Atenolol

Atenolol was commonly sold in the current medical market as both an antihypertensive, diuretic, and anti-angina pectoris drug for customers (Atenolol / CHLORTHALIDONE Prices, coupons & savings tips. GoodRx. (n.d.)). In the market, Atenolol was sold by many different pharmaceutical companies ranging from the cheapest with a price of only $14.83 per prescription for a course of treatment sold by GoodRx to an average retail price of $33.50 in each distinct market dominated by different price elasticity of demand value for medical products (Atenolol / CHLORTHALIDONE Prices, coupons & savings tips. GoodRx. (n.d.)). The price elasticity of demand (PED) is a specific economic index measuring the sensitivity of customer's willingness to purchase a specific product in respond to the change of market price for that product, and in the case of medical markets related to atenolol as an inexpensive prescription drug, the PED value is constantly changing in relationship to the amount of atenolol products throughout the world, making the price of atenolol hard to be standardized due to the constant change in both the economic index and the different private companies responsible for the production of atenolol drug (Price elasticity of demand - harvard university. (n.d.)).

4.2 Canderstan Cilexetil

Canderstan Cilexetil was often sold in the public medical market with a relatively higher price in comparison with atenolol. The standard GoodRx price for canderstan cilexetil is around $23.54 per prescription, and the average retail price for canderstan cilexetil in the modern market is $90.79, which is around 74% higher than the GoodRx standard price. The high price for canderstan cilexetil thus made it an infamous drug in the hypertension market as most patient diagnosed with HTN often lived in a low- and middle-income society where they cannot afford so much money to purchase an almost luxurious drug for the normal prescription treatment (Candesartan prices, coupons & savings tips. GoodRx. (n.d.).). However, a high price and low purchase rate does not mean that canderstan cilexetil has a poor quality over treating HTN. In comparison, canderstan cilexetil do have a better effect over the treatment of HTN than atenolol----their comparison will be discussed furthermore in the next section.

5 DISCUSSION AND CONCLUSION

From a therapeutical perspective, canderstan cilexetil has demonstrated a higher efficiency in treating hypertension than atenolol since it could bind to receptors located in many different parts of the body organs including the adrenal gland and smooth cardiovascular muscle to cease hypertension through both binding sites, while atenolol could only work to stop the increase in blood pressure if it is bond to the correct receptors inside the cardiovascular tissue through the adrenergic pathway. These two drugs are, essentially, very similar in their function mechanism since they both acts as essential blockers for receptors in order to stop high blood pressure, but they still are working in two different systems as atenolol makes its impact. Whereas atenolol functions in the adrenergic system, canderstan works in the renin-angiotensin system to stop both aldosterone and the production of epinephrine to cease hypertension which also marks one merit of canderstan cilexetil on the treatment of hypertension since it could eventually block the production of two high blood pressure-triggering chemicals, while atenolol could only stop the production of one chemical channel in the angiotensin system.

From an economic standpoint, atenolol does looks to have a better foreground than canderstan. Whereas Atenolol has a cheaper price (lowest: $14.83) than canderstan cilexetil (lowest: $23.54), it also has a wider consumer population throughout the globe because of its easy-accessibility and wide production recognized by many medical private companies. As mentioned previously in this literature review, hypertensions most commonly occur in low- and middle-income countries, so many hypertensions diagnosed patients would actually be more apt to choose a more inexpensive medicine for treatment because many of them could not afford to use such a costly medicine like canderstan cilexetil to treat their diagnosed condition. Thus, in conclusion, atenolol and canderstan all have demonstrated their merits distinctively in the perspective of pharmacology or in the field of economy on the behalf of considering for the treatment of hypertension.

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