

Angiotensin Receptor Blocker

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Abstract

Angiotensin II receptor blockers (ARBs) represent a new class of antihypertensive drugs. The mechanism of action of ARB differs from angiotensin-converting (ACE) enzyme inhibitors, which also affect the renin-angiotensin system. The eight ARBs as antihypertensive approved by the FDA were candasartan, telmisartan, valsartan, losartan, irbesartan, eprosartan, olmesartan, azilsartan, while the ninth ARBs approved by the Korea Food and Drug Administration was fimasartan. ARB has a clinical profile that is very similar but it has a different pharmacokinetic profile.

I. INTRODUCTION

The renin angiotensin system plays an important role in regulating blood pressure. Both Angiotensin Converting Enzyme inhibitors (ACEi) and Angiotensin Receptor Blockers (ARBs) have become effective therapies for lowering blood pressure. At the same time the two drugs have a beneficial effect which is to reduce nephropathy progression in patients with diabetes mellitus and chronic heart failure (W.R, Doulton, He, & MacGregor, 2017).

Pharmacology and clinical studies of angiotensin-converting enzyme (ACE) inhibitors, support the idea that Angiotensin II might play a central role not only in the etiology of hypertension but also in the pathophysiology of cardiac hypertrophy and remodeling, heart failure, thickening of blood vessels, atherosclerosis, and glomerulosclerosis in humans (Kim & Iwao, 2017).

A. Molecular Structure Of ARB

Nine types of ARB are available for clinical use worldwide. Although some types of ARB peptides have been synthesized since the 1970s, there are problems with low bioavailability, short duration of action, and partial agonist activity. Losartan non-peptidergic was the first to be developed based on imidazole analogues (Miura, Karnik, & Saku, 2011). Fimasartan, a pyrimidine-4 derivative (3H) from losartan with a substituted imidazole ring, which allows higher potential and a longer duration than losartan (Lee & Oh, 2016). The chemical structure of azilsartan is very similar to the candesartan's structure and differs only from the replacement of 5 members of the tetrazole candesartan ring with 5 oxo-oxadiazole ring members from azilsartan (Antza, Doundoulakis, Stabouli, & Kotsis, 2016).

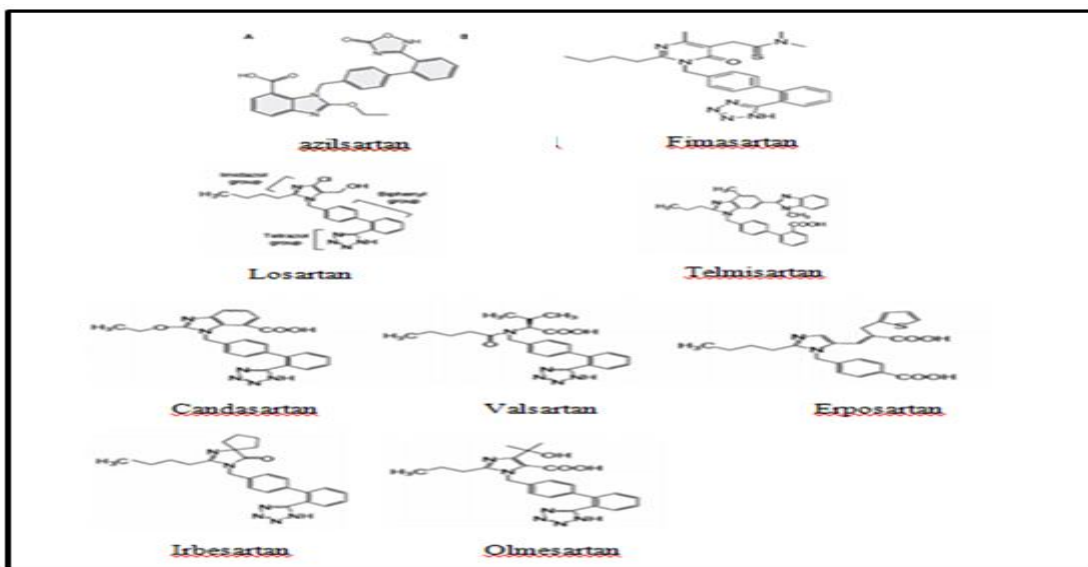


Figure 1. Molecular structure of ARB (Alamanzi, S, Bakheit, H, Asan, & Almatuari, 2018) (Miura, Karnik, & Saku, 2011).

B. Pharmacology Of ARB

Renin is a protease that inhibits angiotensinogen to angiotensin I (ANG I) then will be converted by angiotensin-converting enzyme (ACE) to angiotensin II (ANG II). ANG II binds to two different G-protein-coupled receptors, AT1 and AT2 receptors (AT2R). AT1 receptors are found in many organs and tissues, such as blood vessels, brain, heart, kidneys, adrenal glands and nerve terminals. ANG II signals through the AT1 receptor lead to several effects, all aimed at increasing BP. ANG II leads to systemic vasoconstriction causing an increase in pre-and after-load of the liver. In the kidney, ANG II has a direct effect on reabsorption of sodium in the proximal tubule and an increase in vasopressin which causes increased water reabsorption. Via Mas, ANG (1-7) give vasodilator effects through the release of NO. In addition it also has antifibrotic effects which have the opposite effect with ANG II by preventing cell growth. RAAS antagonists will reduce BP. This principle is used in several classes of antihypertensive drugs (Figure 2) (Marie Hjermitsev, Wehlan, Simonsen, & Kruger, 2017).

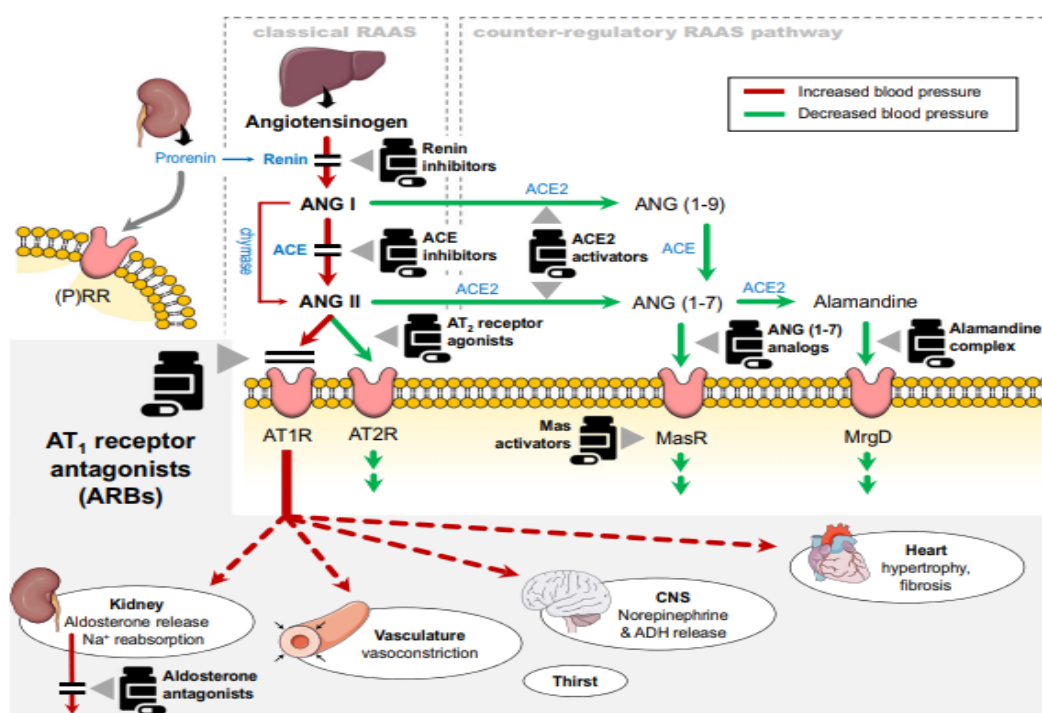


Figure 2. The mechanism of action of ARB (Marie Hjermitsev, Wehlan, Simonsen, & Kruger, 2017).

Almost all aspects of research on AT1 receptors, which are classically considered as the sole mediator of all RAS effects. The AT2 receptor is divided into about 34% of the amino acid sequence homology with the AT1 receptor. AT2 receptor expression is dominant in different brain areas such as locus coeruleus and amygdaloid nucleus. Although the presence of the AT3 receptor subtype displays unique pharmacology, no available literature is available which confirms the presence of different genes for these receptors in humans. High affinity membrane binding for Angiv peptides was referred to as AT4 receptor in 1995. They are concentrated mainly in the brain and at different levels in the heart, kidneys, adrenals and blood vessels. The identity of insulin regulated amino peptidas (IRAP) is thought to be not the only AT4 receptor (Singh & Karnik, 2016).

C. Pharmacokinetics Of ARB

Four ARBs consisted of Losartan Potassium, Candesartan Cilaxetil, Olmesartan Medoxomil, and Azilsartan Medoxomil are prodrug which will be converted into active form in vivo. After oral administration, losartan potassium on the first pass metabolism is converted to EXP3174 in the liver, with about 14% of the dose given being converted into active metabolites. Losartan peak concentration is reached 1 hour after

administration, while EXP3174 reaches the peak level at 3.5 hours. While candesartan cilexetil is completely converted to candesartan by cleavage of the cilexetil portion in the digestive tract during the absorption process and will reach the plasma peak in 4 hours.

Olmesartan medoxomil is a prodrug ester from olmesartan which has strong and long-lasting antihypertensive activity after oral administration. Olmesartan medoxomil is rapidly de-esterified by the arylesterase enzyme located in the small intestine and in the plasma (Park, et al., 2010). Azilsartan medoxomil is a prodrug which is hydrolyzed to azilsartan in the digestive tract. The active part, azilsartan, is an angiotensin II antagonist that selectively blocks the binding of angiotensin II to AT1 receptors in tissues such as vascular smooth muscle and adrenal glands (Micromedex, 2018). Other ARBs such as telmisartan, valsartan, irbesartan, and eprosartan do not include prodrug and are active without bioactivation (Oparil, 2000). The differences in pharmacokinetic characteristics of this ARB are showed in Table 1.

Tabel 1. Pharrmakokinetics of ARB

Parameter	Candasartan Cilexetil (Cagigal, Gonzalez, Alonso, & Jimenez, 2001)	Erposartan (Kumar, Raju, Rao, & Satyanarayana, 2009)	Irbesartan (Husain, Azim, Mitra, & S, 2011)	Losartan Potasium (Bonfilio, Mendonça, Ribeiro, Araújo, & Tarley, 2010) (Burnie & Wuerzner, 2011)	Valsartan (J & H, 2005)	Telmisartan (UJ, G, & B, 1993), (Wienen, et al., 2000)	Olmesartan Medoxomil (Brousil & Burke, 2003)	Azilsartan Medoxomil (Prajapati, Barkate, & Sharma, 2016)	Fimasartan (Kim, Lee, Paik, Kim, & Chi, 2012).
Active metabolit	Yes (Candesartan)	No	No	Yes (EXP3174)	No	No	Yes (Olmesartan)	Yes (Azilsartan)	No
Bioavailability (%)	34-56	13-15	60-80	33	25	30-60	26	60	18,6
Protein binding (%)	99.5	98.0	90.0	98.7	95.0	>98	>99	>99	>97
Elimination	Renal (60%) Biliary (40%)	Renal (10%) Biliary (90%)	Renal (20%) Biliary (80%)	Renal (50%) Biliary (50%)	Renal (30%) Biliary (70%)	Biliary 98%	Renal (40%) Biliary (60%)	Renal (43%) Biliary (57%)	Biliary 97%
Half life	9-12 h	5-7 h	11-15 h	2h	6h	24 h	13h	11h	5.8h
Available dosage	4,8,6,32 mg	200, 300,400mg	75, 150, 300 mg	25,50 mg	80, 160mg	48, 80 mg	20, 40mg	40, 80mg	30,60,120,240 mg
Administration	Oral	Oral	Oral	Oral	Oral	Oral	Oral	Oral	Oral & IV

D. Adverse Reaction Of ARB

In general, ARB can be well tolerated. None of the drugs reviewed has a dose-dependent adverse effect. The frequency of cough was significantly lower in patients taking ARB than in patients taking lisinopril. All ARBs are included in the C category of pregnancy for the first trimester and category D for the second and third trimester (Barreras, Gurk-Turne, & Cheryle, 2003).

II. DRUG INTERACTION

Some ARBs have interactions with diuretics because they can cause a drastic drop in blood pressure so that it can be fatal. The interaction of ARB with other drugs can be seen in Table 2.

Table 2. Drug interaction of ARB.

Drug	Drug interaction
Candesartan Cilexetil (Husin, Azim, Mitra, & Bhasin, 2011)	Diuretics, NSAID, suplemen potassium, Litium
Erposartan (Israili, 2000)	Relatively save given with warfarin, digoxin, glibenclamid, ranitidine.
Irbesartan (Marino & Vachharajani, 2001)	Fluconazole
Losartan Potasium (Inc, 2013)	Diuretics and NSAID (including indomethasin, COX 2)
Valsartan (Siddiqui, Husain, Chaudhry, Alam, Mitra, & Bhasin, 2011)	NSAID and cyclosporine
Telmisartan (Destro, et al., 2011)	ACEI, potassium sparing diuretics, NSAID, heparin, lithium, immunosupresant agent, trimetorpim
Olmesartan Medoxomil (Norwood, III, Smith, & Honeywell, 2002)	Relatively save (not metabolized by P450 cytochrome)
Azilsartan Medoxomil (Dargad, Parekh, Dargad, & Kukrety, 2016)	NSAID and COX 2 inhibitor
Fimasartan (Angeli, Verdecchia, Trapasso, Pane, Signorroti, & Reboldi, 2018)	Atorvastatin, rosuvastatin, digoxin, amlodipine, warfarin, Hydrochlorthiazide, ketokonazole, rifampisin

A. Candesartan Cilexetil

Candesartan is classified as an angiotensin II type 1 antagonist. Angiotensin II type 1 receptor antagonists are widely used in the treatment of diseases such as hypertension, heart failure, myocardial infarction and diabetic nephropathy. Candesartan is lipophilically active orally and has rapid oral absorption (Husin, Azim, Mitra, & Bhasin, 2011).

B. Therapeutic Efficacy

- **Hypertension:** Most antihypertensive effects are seen within 2 weeks of the initial and full dose in 4 weeks. With a once-daily dose, the blood pressure effect ratio is generally more than 80%. Candesartan cilexetil has the effect of lowering blood pressure when taken with hydrochlorothiazide. This positive effect of candesartan can be relevant to vascular protection of patients with essential hypertension (Ghiadoni, Virdis, Magagna, Taddei, & Salvetti, 2000). Candesartan reduces blood pressure and is an effective antihypertensive agent in patients with mild to moderate hypertension. The drug also reduces blood pressure when used in patients with severe hypertension or when used adjunctively in patients with resistant hypertension (Husin, Azim, Mitra, & Bhasin, 2011). AT-1 blockade receptor can partially improve endothelial function by increasing tonic NO release and reducing the vasoconstrictor effect of endogenous ET-1. This positive effect of the study could be relevant to vascular protection of patients with essential hypertension (Ghiadoni, Virdis, Magagna, Taddei, & Salvetti, 2000). The recommended dose is 16 mg once a day. Based on the effect of lowering blood pressure and its side effects, the dose can be increased or lowered. When compared to Losartan, candesartan is more effective in lowering

blood pressure and causing fewer serious side effects than losartan (Zheng, Shi, Jia, Li, & Lin, 2011).

- **Heart failure:** Candesartan can be given to patients with congestive heart failure. Candesartan is a safe and effective choice for patients with systolic heart failure (Ripley, Chonlahan, & Germany, 2006)

C. Eprosartan

Eprosartan is an AII receptor blocker that is very selective towards AT1 receptors. Eprosartan is a drug that is safe and well tolerated without significant interaction. This is important because the possibility of the patient consuming the drug simultaneously (Ruilopec & Jager, 2003). Eprosartan, the only non-biphenyl receptor blocker, non-tetrazole A-II, is a strong, competitive and selective antagonist of the AT-II receptor. Eprosartan is an AT1 vascular receptor (postsynaptically) and at the AT1 presynaptic receptor, where it inhibits the release of noradrenaline which is stimulated sympathetically. The lack of metabolism by cytochrome P450 enzymes results in low potential for metabolic drug interactions and may be important when treating elderly patients and patients with many drugs. In clinical trials, eprosartan has been shown to be as effective in lowering blood pressure as enalapril (ACE inhibitors), and has much lower side effects (Ruilopec & Jager, 2003).

D. Therapeutic Efficacy

Monotherapy: Effective as an antihypertensive drug that can significantly lower blood pressure, especially in patients with mild-severe hypertension regardless of age, sex and race. Long-term administration shows that systolic and diastolic patients are well controlled.

Combination: The combination of eprosartan 600mg with Hydrochlorothiazid 12.5 mg showed a decrease in diastolic blood pressure more than Eprosartan monotherapy. Eprosartan does not have uricosuric properties. Because of eprosartan's lack of uric acid-retaining side effects, it is not possible to present an additional hazard to predominantly stone formation, such as those with a history of nephrolithiasis, volume contraction with low urine flow rates and aciduria (Ruilopec & Jager, 2003) .

E. Irbesartan

Irbesartan is a nonpeptide tetrazole derivative and an angiotensin II antagonist that selectively blocks binding of angiotensin II to the AT1 receptor. Angiotensin II type 1 receptor antagonists are widely used in the treatment of diseases such as hypertension, heart failure, myocardial infarction and diabetic nephropathy. Irbesartan is a specific competitive antagonist of AT1 receptors with far greater affinity (more than 8500 times) for AT1 receptors than AT2 receptors and no agonist activity (Virani, Rajan, Hasumati, & Jain, 2014).

F. Therapeutic Efficacy

- **Hypertension:** Irbesartan is superior for lowering systolic and diastolic BP compared with placebo. Effects occur after administration for 2 weeks and will reach maximum reduction after 2-6 weeks. The combination of angiotensin receptor blockers with hydrochlorothiazide provides additive blood pressure reduction. Diuretics results in a reduction in the body's total sodium by provoking secondary increases in renin, which can compensate for the diuretic and antihypertensive effects.
- **Endothelial effect:** Vasoconstriction triggers oxidative stress, stimulates the release of proinflammatory cytokines and growth factors, and induces a procoagulant state through platelet activation and from plasminogen-activator inhibitors.
- **Diabetic nephropathy:** Irbesartan's efficacy in slowing the development of kidney damage in hypertensive type 2 diabetes patients is clearly shown in PRIME (Program for Irbesartan Mortality and Morbidity Evaluation). There are several arguments to explain this renoprotective effect. Irbesartan has been found to induce renal vasodilation without changing the glomerular filtration rate, to improve endothelial function, and to reduce oxidative stress and inflammation in the kidneys (HH, Lehnert, Brochner-Mortensen, Gomis, & Andersen S, 2001).

E. Losartanpotassium

Losartan potassium is a potent ARB, with angiotensin II type 1 receptor antagonists specific with antihypertensive activity (S.Shanmugam, Chakrahari, K.Sundaramoorthy, T.Ayyappan, & T.Vetrichelvan, 2011).

F. Therapeutic Efficacy

AI1 antagonism with losartan alone or in combination with HCTZ is effective and well-tolerated means of controlling elevated diastolic and systolic blood pressure in patients with mild to moderate hypertension. The efficacy of monotherapy with losartan 50/100 is comparable to that of monotherapy with candesartan 8/16. Significant greater reductions in blood pressure can be achieved by addition of low-dose HCTZ to losartan compared with titration of either candesartan or losartan monotherapy, with no increase in the incidence of adverse events. The present data confirm that losartan, but not candesartan, lowers the serum uric acid level and provides the expected increase in uric acid with HCTZ 12.5 mg in patients with hypertension (Manolis, et al., 2000).

G. Valsartan

Valsartan is an active nonpeptide tetrazole derivative and selectively inhibits Type 1 Receptor Angiotensin II which causes a decrease in blood pressure and is used in the treatment of hypertension (Siddiqui, Husain, Chaudhry, Alam, Mitra, & Bhasin, 2011). Valsartan belongs to the angiotensin II type 1 receptor (AT1) antagonist and has about 20,000 times greater affinity than the angiotensin II type 2 receptor (AT2) (Saydam, 2007). Increased AT2 receptor stimulation causes vasodilation through local production of bradykinin which in turn leads to cascade signals that increase the production of nitric oxide and cyclic guanosine 3'-5-monophosphate at the endothelial level providing protection against vascular dysfunction (P & F, 2004).

H. Therapeutic Efficacy

- **Hypertension:** Giving valsartan 80 mg once a day or with the addition of hydrochlorothiazid effectively reduces systolic and diastolic blood pressure.
- **Cronic Heart Failure:** Valsartan is a good treatment for patients with hypertension receiving ACE inhibitors. In addition Valsartan reduced hospitalization (27.5%) in CHF patients (KC & C, 2009). Valsartan appears to be better tolerated in context with side effects like cough and angioedema as seen with the ACE inhibitors (Siddiqui, Husain, Chaudhry, Alam, Mitra, & Bhasin, 2011).
- **Renal Impairment:** Giving valsartan to patients with renal impairment shows a decrease in proteinuria (26%) and albuminuria (41%) (J & H, 2005).

I. Telmisartan

Telmisartan is a potent, long-lasting, nonpeptide antagonist from the angiotensin II type-1 (AT1) receptor indicated for the treatment of essential hypertension selectively and inhibit stimulation of AT1 receptors unresolved by receptors by angiotensin II without affecting other receptor systems involved in cardiovascular regulation. Telmisatrtan activates PPAR- γ and opposite AT1 receptors; thus, it has a greater beneficial effect on glucose and lipid metabolism than other ARBs. Some studies classify telmisartan as 'metabolic sartan'. Metabolic sartan that improves insulin resistance and dyslipidemia can provide more effective options for preventing end-organ damage and cardiovascular disease in patients with hypertension (Inoue & Node, 2008).

J. Therapeutic Efficacy

Telmisartan has emerged as the most widely used ARB among all ARBs, for the majority of hypertensive and comorbid patients (Ramakrishna, Ingole, Dey, & Jain, 2017). Improvement of insulin sensitivity and lipid profile in hypertensive patients with or without type 2 diabetes and metabolic syndrome (effect of that of losartan and eprosartan, but not significantly different from valsartan, irbesartan and nifedipine (Destro, et al., 2011). Effect on cardiovascular system is Lowering BP reduction of LVH, prevention of recurrence of atrial fibrillation in hypertensive patients. Compared with losartan 50 mg, telmisartan 40 mg or 80 mg telmisartan has superior control of both SBP and DBP during the last 6 h of the dosing interval. Another study has also compared telmisartan 80 mg with valsartan 80 mg after treatment for 8 weeks for detecting greater reduction in the last 6 h mean DBP in telmisartan-treated patients (7.5 mm Hg vs. 5.2 mm Hg). Four

hours after being consumed in the morning, Telmisartan can reduce SBP/DBP. Long-term use can reduce 10mmHg SBP and 5mmHg DBP. In addition, the use of telmisartan can reduce the risk of death by about 40% due to stroke and 30% due to ischemic heart disease and other vascular diseases (Gosse, 2006).

K. Olmesartan Medoxomil

Olmesartan is an angiotensin II receptor antagonist that has a mechanism like Losartan. Oral administration of Olmesartan is as Olmesartan Medoxomil prodrug ester. After 1 dose administration, hypotension will occur after 24 hours, where the hypotensive effect will be achieved after 2 weeks of therapy and will be maximal at week 8. After oral administration, olmesartan medoxomil is extracted in the intestinal tract to produce active olmesartan metabolites and do not undergo additional metabolic changes. The antihypertensive efficacy of olmesartan medoxomil can occur from unique pharmacological interactions of the drug with the AT1 receptor, resulting in strong, long-lasting A-II blockade, and dependent on dosage (Al-Majed, Bakheit, Aziz, & Al-Jallal, 2017).

L. Therapeutic Efficacy

Olmesartan providing a vasoprotective effect by reducing oxidative stress mediated by Ang II and increasing endothelial repair mediated by CGRP dysfunction. Olmesartan increases the number of EPCs and improved survival function. Besides that, Olmesartan has the potential effect of antioxidants and anti-inflammation, after long-term use. Olmesartan also provides antiatherosclerotic effects and antiremodeling effects (Calo, et al., 2014). In a meta-analysis, it was proved that azilsartan was superior in dealing with essential hypertension in reducing SBP compared to Olmesartan (Zhao, Liu, & Dong, 2018).

M. Azilsartan Medoxomil

Azilsartan medoxomil is the eighth drug in this group, which has been approved by the FDA for the treatment of hypertension. It is used orally, alone or in combination with other antihypertensive drugs (Handley, Lloyd, Roberts, & Barger, 2016). Azilsartan medoxomil with a dose of 40 mg and 80 mg proved to be effective for treating essential hypertension (Juhaz, Wu, Hisada, Tsukada, & Jueng, 2018). Azilsartan has a 10,000-fold greater affinity for AT1 receptors, compared to binding with AT2 receptors. The regulation of negative angiotensin II feedback on renin secretion is also inhibited, resulting in an increase in plasma renin concentration and consequently an increase in plasma angiotensin II concentration (Micromedex, 2018).

N. Therapeutic Efficacy

No dosage adjustments are needed for patients with special populations, such as elderly, renal impairment (mild to moderate), and hepatic impairment (mild to moderate). Azilsartan can reduce BP in patients with grade I essential hypertension. In addition to being effective in reducing BP in hypertensive adults, azilsartan also shows several pleiotropic effects in in vitro studies. A study in obese mice with spontaneous hypertension, aside from BP reduction, treatment with azilsartan reduced basal plasma insulin concentrations and an assessment of the insulin resistance homeostasis model index. In adipose epididymal tissue, azilsartan also induces adipocyte differentiation and decreased adipose tissue weight and adipocyte size by increasing the expression of adiponectin, PPARc, CCAAT/binding protein and adipocyte 2 gene protein in adipose tissue. This beneficial effect of azilsartan may play a role in the treatment of metabolic syndrome.

Azilsartan also uses antiproliferative effects through vascular inhibition and aortic endothelial cell proliferation in the absence of exogenously added angiotensin II. In preclinical studies, azilsartan facilitates the stabilization of atherosclerotic plaques by suppressing vascular wall expression of type I protein plasminogen activator inhibitors and suppressed cardiac remodeling and develops into heart failure after myocardial infarction in male rats. This beneficial effect of azilsartan can prove its role in the treatment of cardiovascular disease (Prajapati, Barkate, & Sharma, 2016).

O. Fimasartan

Fimasartan is the ninth and newest ARB approved as an antihypertensive drug by Korean Food and Drug Administration (Lee & Oh, 2016). Fimasartan has been shown to effectively reduce blood pressure after single or repeated oral and intravenous administration and show superior inhibitory activity compared to other ARBs such as losartan and candesartan. Fimasartan has greater affinity for the AT1 receptor subtype than losartan in the radioligand binding assay and do not show a partial agonist effect on angiotensin II receptors in other in vivo studies using hypertensive animals (Kim, et al., 2014).

P. Therapeutic Efficacy

Fimasartan 60-120 mg once daily shows an antihypertensive effect for 24 hours. In a study with large populations, fimasartan showed an excellent safety profile, also various preclinical studies have shown its anti-inflammatory effects. The efficacy and tolerability of the fimasartan was compared with losartan in a 12-week, phase III, multicenter, prospective, randomized, double-blind clinical trial. In that study the fimasartan group showed a significant greater BP reduction than the losartan group. Another phase II study of the combination of masonry with hydrochlorothiazide, the magnesium/hydrochloride combination treatment group showed a greater reduction of BP than the monotherapy group. The combination treatment also has comparable safety and tolerance to fimasartan monotherapy (Lee & Oh, 2016).

III. CONCLUSION

ARBs have very similar clinical profiles but they have differences in pharmacokinetic profiles. Four ARBs are losartan potassium, candesartan cilexetil, olmesartan medoxomil, azilsartan medoxomil are prodrug which will be converted into active form in vivo, so that it takes longer to become active form and give therapeutic effect.

Valsartan as antihypertensive agent in patients with proven renal impairment can reduce proteinuria and albuminuria significantly. Erposartan is relatively safe when used with other drugs because it does not inhibit cytochrome P450, so it can significantly reduce drug interactions. Fimasartan is the latest ARB whose research is still limited and has not been widely used for hypertension therapy. In addition, fimasartan is the only ARB in the form of injection.

Irbesartan is an ARB with the highest bioavailability when compared to other ARBs which is around 60-80%, where food does not interfere with drug absorption. Irbesartan also has a renoprotector effect in hypertensive patients with type 2 diabetes mellitus. It is really beneficial to prevent the occurrence of diabetic nephropathy.

Telmisartan was chosen as the most widely used ARB by clinicians for the treatment of hypertension with comorbid disease, due to the long half-life so that the frequency used is once a day, thus can improve patient compliance. Long-term use of Telmisartan can reduce 10mmHg SBP and 5mmHg DBP. Besides, telmisartan is also a metabolic sartan that can improve insulin resistance and dyslipidemia so that it is a more effective choice to prevent end-organ damage and cardiovascular disease in patients with hypertension.

Reference

- Alamanzi, A., S, A., Bakheit, A. H., HASan, E., & Almatuari, M. S. (2018). Spectroscopic and molecular docking studies of the binding of the angiotensin II receptor blockers (ARBs) azilsartan, eprosartan and olmesartan to bovine serum albumin. *Journal of luminiscence*, 616-628.
- Al-Majed, A. A., Bakheit, A. H., Aziz, H. A., & Al-Jallal, A. A. (2017). Olmesartan. *Profiles of Drug Substances, Excipients, and Related Methodology*, Volume 42, 241-282.
- Angeli, F., Verdecchia, P., Trapasso, M., Pane, M., Signorroti, S., & Reboldi, G. (2018). PK/PD evaluation of fimasartan for the treatment of hypertension Current evidences and future perspectives. *Expert Opinion on Drug Metabolism & Toxicology*.
- Antza, C., Doundoulakis, I., Stabouli, S., & Kotsis, V. (2016). Azilsartan, a promising Angiotensin II Receptor Blocker in the management of hypertension . *Hellenic Atherosclerosis Society*, 53-62.
- Barreras, A., Gurk-Turne, & Cheryle. (2003). Angiotensin II receptor blockers. *Bumc Proceeding*, 123-126.
- Bonfilio, R., Mendonça, T. F., Ribeiro, G., Araújo, M. B., & Tarley, C. R. (2010). Losartan potassium dissolution test for drug release evaluation in pharmaceutical capsules using HPLC and UV spectrophotometry. *Quím. Nova* vol.33.
- Brousil, J. A., & Burke, J. M. (2003). Olmesartan Medoxomil An Angiotensin II-Receptor Blocker. *Excerpta medica*, 1041-1055.

- Burnie, M., & Wuerzner, G. (2011). Pharmacokinetic evaluation of losartan. *informa helathcare*, 643-649.
- Calo, L. A., Maso, L. D., Pagnin, E., Ravarotto, V., Facco, M., Boscaro, E., et al. (2014). Effect of olmesartan medoxomil on number and survival of circulating endothelial progenitor cells and calcitonin gene related peptide in hypertensive patients. *Journal of Hypertension*, 193-199.
- Dargad, R. R., Parekh, J. D., Dargad, R. R., & Kukrety, S. (2016). Azilsartan: Novel Angiotensin Receptor Blocker. *Journal of The Association of Physicians of India* Vol. 64.
- Destro, M., Cagnoni, F., Dognini, G. P., Galimberti, V., Taietti, C., C. C., et al. (2011). Telmisartan: just an antihypertensive agent? A literature review. *Informa healthcare*, 2719-2735.
- Forni, v., wuerzner, G., Pruijm, M., & Burnier, M. (2011). Long-term use and tolerability of irbesartan for control of hypertension. *Integrated Blood Pressure Control*, 17-26.
- Ghiadoni, L., Virdis, A., Magagna, A., Taddei, S., & Salvetti, A. (2000). Effect of the Angiotensin II Type 1 Receptor Blocker Candesartan on Endothelial Function in Patients With Essential Hypertension. *American Heart association*, 501-506.
- Gosse, P. (2006). A review of telmisartan in the treatment of hypertension: blood pressure control in the early morning hours. *Vascular Health and Risk Management*, 195-201.
- Handley, A., Lloyd, E., Roberts, A., & Barger, B. (2016). Safety and tolerability of azilsartan medoxomil in subjects with essential hypertension: a one-year, phase 3, open-label study. *Clin Exp Hypertens*, 180-188.
- HH, P., Lehnert, J., Brochner-Mortensen, J., Gomis, R., & Andersen S, A. P. (2001). The effect of irbesartan on the development of diabetic nephropathy in patients with type 2 diabetes. *N Engl J Med*, 870-878.
- Husain, A., Azim, M. S., Mitra, M., & S, P. (2011). A review of pharmacological and pharmaceutical profile of irbesartan. *Pharmacophore An International Research Journal*, 276-286.
- Husin, A., Azim, M. S., Mitra, M., & Bhasin, P. S. (2011). A Review on Candesartan: Pharmacological and Pharmaceutical Profile. *Journal of Applied Pharmaceutical Science*, 12-17.
- Inc, A. P. (2013). product monograph 'AURO LOSARTAN'. 1-41.
- Inoue, T., & Node, K. (2008). Telmisartan as a metabolic sartan for targeting vascular failure. *Informa healthcare*, 1397-1406.
- Israili, Z. (2000). Clinical pharmacokinetics of angiotensin II (AT1) receptor blockers in hypertension. *Journal of Human Hypertension*, 73-86.
- J, M., & H, K. (2005). Role of Valsartan and other angiotensin receptor blocking agents in the management of cardiovascular disease. *Pharmacol Res*, 203-212.
- Juhaz, a., Wu, j., Hisada, M., Tsukada, T., & Jueng, M. H. (2018). Efficacy and safety of azilsartan Medoxamil, an angiotensin receptor blocker, in Korean patients with essential hypertension. *clinical hypertension*.
- KC, F., & C, T. (2009). The Management of Hypertension With Angiotensin Receptor Blockers in Special Populations. *Clin Cornerstone*, s5-s17.
- Kim, J. H., Lee, J. H., Paik, S. H., Kim, J. H., & Chi, Y. H. (2012). Fimasartan, a Novel Angiotensin II Receptor Antagonist. *Arch Pharm Res* Vol 35, 1123-1126.
- Kim, S., & Iwao, H. (2017). Molecular and Cellular Mechanisms of Angiotensin II-Mediated Cardiovascular and Renal Diseases. *ASPET*.

- Kim, T. H., Shin, S., Bashir, M., Chi, Y. H., Paik, S. H., Lee, J. H., et al. (2014). Pharmacokinetics and metabolite profiling of fimasartan, a novel antihypertensive agent, in rats. *Xenobiotica*, 913-925.
- Lee, H.-Y., & Oh, B.-H. (2016). Fimasartan: A New Angiotensin Receptor Blocker. *Drugs*, 1015-1022.
- Manolis, A. J., Grossman, E., Jelakovic, B., Jacovides, n., Bernhardt, D. C., Cabrera, W. J., et al. (2000). Effects of Losartan and Candesartan Monotherapy and Losartan/Hydrochlorothiazide Combination Therapy in Patients with Mild to Moderate Hypertension. *Clinical Therapeutic* vol. 22, NO. 10, 1186-1203.
- Marie Hjermitslev, D. G., Wehlan, M., Simonsen, U., & Kruger, M. (2017). Azilsartan Medoxomil, an Angiotensin II Receptor Antagonist for the Treatment of Hypertension. *Basic & Clinical Pharmacology & Toxicology*, 225-233.
- Marino, M., & Vachharajani, N. (2001). Drug interactions with irbesartan. *Clin Pharmacokinet*, 605-614.
- Micromedex. (2018). www.micromedex.com. Retrieved September 2018
- Miura, S.-i., Karnik, S. S., & Saku, K. (2011). Angiotensin II type 1 receptor blockers: class effects versus molecular effects. *Journal of The renin angiotensin aldosterone system*, 1-7.
- Norwood, D., III, E. B., Smith, B., & Honeywell, M. (2002). Olmesartan Medoxomil for Hypertension: A Clinical Review. *DRUG FORECAST* vol 27, 611-618.
- Oparil, S. (2000). Newly Emerging Pharmacologic Differences in Angiotensin II Receptor Blockers. *American Journal of Hypertension*, 18-24.
- P, V., & F, A. (2004). Assessment of the optimal daily dose of valsartan in patients with hypertension, heart failure, or Both. *Clin Therapeutics*, 460-472.
- Park, J.-H., Chang, J.-S., El-Gamal, M. I., Choi, W.-K., Lee, W. S., Chung, H. J., et al. (2010). Novel amides and esters prodrugs of olmesartan: Synthesis, bioconversion, and pharmacokinetic evaluation. *Bioorganic & Medicinal Chemistry Letters* 20, 5895-5899.
- Prajapati, H., Barkate, H., & Sharma, R. (2016). Azilsartan: from bench to bedside. *Drugs Ther Perspect*, 343-350.
- Ramakrishna, S., Ingole, S., Dey, A., & Jain, R. (2017). Management of Hypertension: Insights into Prescribing Behavior with Focus on Angiotensin Receptor Blockers. *Journal of the Practice of Cardiovascular Sciences*, 22-27.
- Ripley, T. L., Chonlahan, J. S., & Germany, R. E. (2006). Candesartan in heart failure. *Clinical Interventions in Aging*, 357-366.
- Ruilope, L., & Jäger, B. (2003). Eprosartan for the treatment of hypertension. *Ashley Publications*, 107-114.
- S.Shanmugam, Chakrahari, R., K.Sundaramoorthy, T.Ayyappan, & T.Vetrichelvan. (2011). Formulation and Evaluation of Sustained Release Matrix Tablets of Losartan potassium. *International Journal of PharmTech Research*, 526-534.
- Saydam, T. (2007). Bioavailability File: Valsartan. *FABAD J Pharm Sci*, 185-196.
- Siddiqui, N., Husain, A., Chaudhry, L., Alam, M. S., Mitra, M., & Bhasin, P. S. (2011). Pharmacological and Pharmaceutical Profile of Valsartan: A Review. *Journal of Applied Pharmaceutical Science* 01 (04), 12-19.
- Singh, K. D., & Karnik, S. S. (2016). Angiotensin Receptors: Structure, Function, Signaling and Clinical Applications. *J Cell Signal*.

- UJ, R., G, M., & B, N. (1993). 6-Substituted benzimidazoles as new nonpeptide angiotensin II receptor - antagonists: Synthesis, biological activity, and structure-activity relationships. *J Med Chem*, 4040-4051.
- Virani, P., Rajanit, S., Hasumati, R., & Jain, V. (2014). Irbesartan: A Review on Analytical Method and its Determination in Pharmaceuticals and Biological Matrix. *Inventi Journals* , 1-8.
- W.R, T., Douulton, He, F. J., & MacGregor, G. A. (2017). Systematic Review of Combined Angiotensin-Converting Enzyme Inhibition and Angiotensin Receptor Blockade in Hypertension. *American Heart Association*, 880-885.
- Wienen, W., Entzeroth, M., Meel, J. C., Stangier, J., Busch, U., Ebner, T., et al. (2000). A Review on Telmisartan A Novel, Long-Acting Angiotensin II-Receptor Antagonist. *Cardiovascular Drug Reviews vol 18*, 127-154.
- Zhao, D., Liu, H., & Dong, P. (2018). Antihypertensive effect of azilsartan versus olmesartan in patients with essential hypertension: a meta-analysis. *Irish Journal of Medical Science*.
- Zheng, Z., Shi, H., Jia, J., Li, d., & Lin, S. (2011). A systematic review and meta-analysis of candesartan and losartan in the management of essential hypertension. *Journal of the Renin-Angiotensin aldosteron system*, 365-374.
- Cagigal, E., Gonzalez, L., Alonso, R., & Jimenez, R. (2001). pKa determination of angiotensin II receptor antagonistic (ARA II) by spectrofluorimetry. *J Pharm Biomed Anal*, 477-486.
- Kumar, K., Raju, A., Rao, J. S., & Satyanarayana, T. (2009). The estimation of eprosartan mesylate in pharmaceutical dosage forms by RP-HPLC. *Oriental Journal of Chemistry*, 711-714.