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Review Article

Angiotensin II Receptor Antagonists: The Utility of the Therapeutic Agents in Clinical Practice

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Received: August 16, 2022; **Published:** August 30, 2022

Abstract

Clinical treatment of hypertension with potent antihypertensive agents is very vital to avoid the risks of heart failure, myocardial infarction, stroke and chronic renal failure occurring. The current antihypertensive treatment regimens involve the use β-blockers, diuretics (mostly thiazides), calcium channel blockers, angiotensin converting enzyme inhibitors and angiotensin II receptor antagonists. Of all these therapeutic agents, angiotensin II receptor antagonists have major advantage over others which is exceptional good tolerability profile, that may enhance compliance and persistency with treatment.

Combination of low-dosed diuretics with angiotensin II receptor antagonists will permit maximum benefit from potassium depletion, control of the compensatory increase in renin secretion, resulting in the enhancement of the efficacy and safety of these antagonists. Finally, therapeutic effectiveness, tolerability and safety profile have made angiotensin II receptor antagonists drugs mostly utilized in clinical practice for the treatment of hypertension and in some cases diabetic neuropathy.

Keywords: *Hypertension; Angiotensin II Receptor Antagonists; Clinical Utilization*

Introduction

Blood pressure is one of the most vital and prevalent risk factors for cardiovascular disease causing global morbidity and mortality. The disorder can lead to myocardial infarction, heart failure, stroke and chronic renal failure if not effectively controlled [1].

Renin-angiotensin-aldosterone system is one of the mechanistic pathways of blood pressure increase. It plays a vital role in modulating cardiovascular function as well as in the pathophysiology of cardiac hypertrophy, heart failure, hypertension and vascular disease [2,3], Renin (in the kidney), is a proteolytic enzyme that acts on angiotensinogen (a plasma protein) to catalyze the formation of angiotensins. Of all the angiotensin types, angiotensin I (a decapeptide) and angiotensin II (an octapeptide) are the most important. Angiotensin II is obtained from angiotensin I by the action of catalyzing enzyme called angiotensin-converting enzyme [4]. Angiotensin II (a potent vasoconstrictor) stimulates aldosterone synthesis, cardiac contraction, sympathetic nervous system activity, secretion of aldosterone by adrenal cortex, and renal reabsorption of sodium [5,6]. Its pressor effects are mediated by the AT1 subtype receptor.

Inhibition of the renin-angiotensin-aldosterone system will provide beneficial effects in the hypertensive patients. Angiotensin II receptor antagonists inhibit renin-angiotensin-aldosterone system and are the newest class of antihypertensive agents. They act by selectively blocking the binding of AT II to AT1 receptor thus generating more blockade of the renin - angiotensin - aldosterone system [7]. AT1 receptors mediate the endothelin secretion, aldosterone and vasopressin release, vasoconstriction, suppression of renin secretion, sodium retention, and activation of the sympathetic nervous system [8].

A number of these angiotensin II receptor antagonists are in clinical use and they include: candesartan, eprosartan, irbesartan, losartan, olmesartan, telmisartan and valsartan.

In the present article, we shall provide the pharmacological and toxicological properties of the angiotensin II receptor antagonists as well as consider their utilities in clinical practice.

Irbesartan is a potent, noncompetitive, long acting angiotensin II receptor antagonist and is specific for the AT1 receptor subtype [9]. Chemically, it is defined as (2-butyl-3-({4-[2-(2H-1,2,3,4-tetrazol-5- yl)phenyl]phenyl}methyl)-1,3-diazaspiro[4.4]non-1-en-4-one, Irbesartan acts by selectively binding to AT1receptor, thus blocking the vasoconstrictor and aldosterone-secreting effects of angiotensin II.

Pharmacodynamics

The pharmacodynamics of the drug shows that it is used clinically in the treatment of hypertension and diabetic nephropathy in hypertensive patients with type 2 diabetes, elevated serum creatinine and proteinuria. The inhibitor effect is dose-dependent and 100% inhibition can be obtained after 2 - 4h of drug administration. Monotherapy with irbesartan (150 - 300 mg/day) generated blood pressure normalization in about 70% of hypertensive patients. Combination with diuretics such as hydrochlorothiazide (HCTZ) attenuates the potassium loss, usually associated with HCTZ therapy [10].

Pharmacokinetics

The pharmacokinetics of irbesartan depict that it is well absorbed and the bioavailability is not affected by food. At a single oral dose of 150 mg irbesartan has (i) peak plasma concentration (C_{max}) of 1.9 mg/l, (ii) time to reach C_{max} (T_{max}) of 1.5h; (iii) area under curve in time versus plasma concentration curve (AUC) of 9.7 mg/h/l, (iv) bioavailability of 61%, (v) elimination half-life (t½) of 16h, (vi) 90% bound to serum proteins, (vii) average volume of distribution of 53 - 93L, (viii) total plasma and renal clearances are in the range of 157 - 176 ml/min (9-11 L/h) and 3 ml/min (0.18 L/h), respectively. However, for 300 mg oral dose of the drug; the C_{max} is 2.9 mg/l; the T_{max} is 1.5h, AUC is 20 mg/h/l; and the t½ is 14h [10]. The drug is metabolized via glucuronide conjugation and oxidation. Inactive irbesartan glucuronide conjugate is the primary circulating metabolite. Irbesartan has no relevant interaction with other drugs since it is metabolized by cytochrome P450 (CYP)2C9 [11,12].

Clinical efficacy

Irbesartan is very effectively used in hypertension, heart failure and nephropathies. Doses of 150 - 300 mg/day have shown proven efficacy for mild-to-moderate hypertension treatment and also has end-organ protective effects, namely nephroprotective actions. Due to its usefulness for other pharmacological indications, its clinical efficacy can be evaluated under two major headings namely blood pressure-lowering efficacy and end-organ protection [13,14].

Side effects

The potential side effects of irbesartan include headache, fatigue, dizziness, diarrhea, heartburn, dyspepsia, tachycardia and anxiety, musculoskeletal pain, upper respiratory infection [15,16].

Losartan

Losartan is the first approved of a new class of potent and selective nonpeptide AII receptor antagonists. Chemically defined as 2-butyl 4 chloro-5-hydroxymethyl-1-{[2′ (1h tetrazol 5 yl)biphenyl-4- yl]methyl}imidazole. It acts by inhibiting the vasoconstrictor and aldosterone-secreting effects of angiotensin II selectively through AT1 receptor.

Pharmacodynamics

Losartan increases urinary output. It also reduces the risk of stroke in patients with hypertension and left ventricular hypertrophy. The standard dose is 0.7 mg/kg once daily to a maximum of 50 mg/day, but adjustments may be necessary according to patient blood pressure response. The dosing range is 25 - 100 mg per day in 1 or 2 divided daily doses. Dosing may need to be decreased to 25 mg once daily in patients with volume depletion, renal insufficiency, or hepatic impairment [17].

Pharmacokinetics

The pharmacokinetics of losartan indicates that food slows absorption; decreases C_{max}, but has minor effects on the AUC of the drug. At a single oral dose of 50 mg losartan has (i) peak plasma concentration (C_{max}) and area under the concentration versus time curve to infinity proportional to the dose, (ii) time to reach C_{max} (T_{max}) of 1h; (iii) bioavailability of 33%, (iv) elimination half-life (t½) of 1.5 - 2h, (v) a renal clearance of 75 ml/min, (vi) 98.7% bound to serum proteins, (vii) average volume of distribution of 34L, (viii) total body clearances of 600 ml/min, (ix) renal excretion of 35% (4% unchanged, 6% as active metabolite), (x) fecal excretion of 60%. Its hepatic metabolism involves extensive first-pass metabolism via CYP2C9 and 3A [18].

Clinical efficacy

Losartan is effectively used in hypertension, diabetic nephropathy. It reduces the risk of stroke in patients with hypertension and left ventricular hypertrophy. Losartan efficacy may be decreased if co-administered with nonsteroidal anti-inflammatory drugs [19].

Side effects

The most common potential side effects include dizziness, chest pain, fatigue, headache, hypoglycemia, hyperuricemia, hyperkalemia, diarrhea, urinary tract infection, anemia and cough, with most occurring more frequently in patients taking the drug for treatment of diabetic nephropathy. Other side effects may include hepatitis, malaise, thrombocytopenia, angioedema, hypersensitivity, hyperkalemia, hyponatremia, rhabdomyolysis, dysgeusia, dry cough and erythroderma [20].

Valsartan

Valsartan as a member of angiotensin II receptor antagonist, competitively and selectively inhibits the actions of angiotensin II at the AT1 receptor subtype. It is chemically defined as S-N-Valeryl-N-[(2'-1H-tetrazol-5-yl)bi phenyl-4-yl]methyl valine.

Pharmacodynamics:

At a single dose of 80 mg, valsartan is an effective antihypertensive agent in both mild to moderate and severe hypertension. Combination with diuretics such as hydrochlorothiazide (HCTZ) at 12.5 mg or 25 mg has increased the antihypertensive activity and control rates in most patients [21].

Pharmacokinetics

At a single oral dose of 80 mg valsartan has (i) peak plasma concentration (C_{max}) of 1.64 mg/l, (ii) time to rea86ch C_{max} (T_{max}) of 2h; (iii) bioavailability of 23%, (iv) elimination half-life (t½) of 7 - 8h, (v) 95% bound to serum proteins, (vi) average volume of distribution of 17L, (vii) plasma clearances of 2 L/h, (viii) urine excretion of less than 20%, (ix) biliary excretion of greater than 80%. Not metabolized by cytochrome P450 enzymes [22].

Clinical efficacy

Valsartan doses of 80 - 160 mg/day have shown proven efficacy for mild-to-moderate hypertension treatment, heart failure and acute myocardial infarction. The efficacy is dose related in both geriatric and younger patients [23].

Side effects

Potential side effects include dizziness or lightheadedness, headache, and abdominal pain [24].

Telmisartan

Telmisartan is another angiotensin II receptor antagonist used in the management of hypertension. It acts by interfering with the binding of angiotensin II to the angiotensin II AT1-receptor. Its reversibly and selectively bind to the receptors in vascular smooth muscle and the adrenal gland ultimately leading to arterial blood pressure reduction Chemically, it is defined as 4' [[2 propyl-4- methyl-6-(1methylbenzimidazol 2 yl)benzimidazol-1-yl]methyl]biphenyl-2- carboxylic acid.

Pharmacodynamics

Telmisartan following oral administration is absorbed rapidly from the gastrointestinal tract. The recommended starting dose is 40 mg once daily. Approximately one half of orally administered dose is absorbed. The antihypertensive effect of the drug is greater in antihypertensive patients with higher plasma renin activity. As a partial agonist of PPARγ, (target for antidiabetic drugs), it can improve carbohydrate and lipid metabolism, as well as control insulin resistance [25].

Pharmacokinetics

The pharmacokinetics of telmisartan indicates that food reduces AUC of the drug. At a single oral dose of 40 mg telmisartan has (i) peak plasma concentration (C_{max}) and area under the concentration versus time curve to infinity proportional to the dose, (ii) time to reach C_{max} (T_{max}) of 0.5 - 1h; (iii) bioavailability of 42% or 58% (for 160 mg dose), (iv) elimination half-life (t½) of 24h, (v) > 99% bound to serum proteins, (vi) volume of distribution of 500 ml, (vii) total body clearances is > 800 ml/min, (viii) urine excretion of about 0.91%, (xi) biliary excretion of unchanged drug is 87%. A very small fraction of the drug undergoes metabolism to glucuronide derivative. Its metabolism does not involve cytochrome P450 isoenzymes [26].

Clinical efficacy

Telmisartan is effective when used alone or in combination with other classes of antihypertensives for the treatment of hypertension. It is effective also in the treatment of diabetic nephropathy in hypertensive patients with type 2 diabetes mellitus, as well as in congestive heart failure treatment [27].

Side effects

The potential side effect of telmisartan include allergic reaction such as hives; difficulty in breathing, swelling of the face, throat or tongue, stuff nose, anuria, rapid weight gain, pain (back, chest, sinus), hyperkalemia [28].

Eprosartan

Eprosartan is a potent, nonphenyl, nontetrazole angiotensin II receptor antagonist with a high degree of affinity for AT receptor sites. It is chemically defined as (E)-α-[[2-butyl-1-[(4-carboxyphenyl)methyl]-1Himidazol-5-yl]methylene]-2-thiophenepropanoic acid. The drug

is the only angiotensin II receptor antagonists which does not have a biphenyl tetrazole moiety. Unlike most other angiotensin II receptor antagonists, eprosartan acts as a pure competitive antagonist.

Pharmacodynamics

Eprosartan reduces hypertension by antagonizing the effect of angiotensin II on blood pressure, renal blood flow and aldosterone secretion. Following oral administration at a dose of 600 mg eprosartan once daily, blood pressure control is maintained over a 24-hour period with no first dose postural hypotension or reflex tachycardia. Eprosartan may be taken with or without food. No rapid rebound increase in blood pressure following discontinuation of treatment with eprosartan [29].

Pharmacokinetics

The pharmacokinetics of eprosartan following single oral administration depicts it to have incomplete oral absorption and food intake appears to have unpredictable effect. At a single oral dose of 100 mg eprosartan has (i) peak plasma concentration (C_{max}) and area under the concentration versus time curve to infinity have proportional relationship to the dose, (ii) time to reach C_{max} (T_{max}) of 1 - 3h, (iii) 98% bound to serum proteins About 90% of orally administered eprosartan is found in the feces and the remainder found in the urine. Of the excreted drug only 20% undergoes metabolism to its glucuronide form. The drug is not metabolized by the cytochrome P450 system [30].

Clinical efficacy

Eprosartan is effective for the treatment of essential hypertension. Eprosartan may be used alone but additive effect occurs when given in combination with hydrochlorothiazide or a calcium channel blocker. Duration of treatment is not limited and no dose adjustment is required in geriatric patients [30].

Side effects: They may include asthenia, allergic skin reactions (rash, pruritus) dizziness, arthralgia, cough, diarrhea, headache and rhinitis [29].

Candesartan cilexetil

Candesartan cilexetil is the prodrug of candesartan, an angiotensin II type 1 (AT1) receptor antagonist. Chemically defined as (1RS)-1-[[(Cyclohexyloxy)carbonyl]oxy]ethyl 2-ethoxy-1-[[2′-(1H-tetrazol-5- yl)biphenyl-4-yl]methyl]-1H-benzimidazole-7-carboxylate.

Pharmacodynamics

Following an oral administration of dosages range between 8 and 32 mg/day, absorbed candesartan cilexetil is completely metabolized to candesartan. In patients with hypertension, the response rate of monotherapy with candesartan increases with the dose, but never exceeds 60% at a daily dosage of 16mg of candesartan. However, at 32 mg/day dose the response rate does not increase [31].

Pharmacokinetics

Candesartan is an active metabolite of candesartan cilexetil (prodrug). Food does not affect the pharmacokinetics of the drug. At a single oral dose, candesartan cilexetil has (i) an incomplete absorption from the gastrointestinal tract resulting in an oral bioavailability of about 15% (ii) elimination half-life (t½) of > 9h at 8 mg dose, (iii) > 90% bound to serum proteins, (iv) volume of distribution of 0.13 L/kg [32].

Clinical efficacy

Treatment with candesartan cilexetil has shown to be very effective and well tolerated in patients with mild to moderate primary hypertension. The efficacy of candesartan cilexetil is independent of antihypertensive co-administration [33].

Side effects

Potential side effects include dizziness, musculoskeletal pain [31].

Olmesartan medoxomil is a potent, competitive and selective angiotensin II antagonist. It acts by selectively blocking the binding of angiotensin II to the AT1receptor in vascular smooth muscle. It is defined as 4-(2hydroxypropan-2yl)2-propyl1-({4-[2-(1H-1-tetrazol-5-ylphenyl]phenyl}methyl)-1-imidazole-5-carboxylicacid.

Pharmacodynamics

Olmesartan medoxomil following once daily administration at doses of 10-80 mg showed dose-dependently reduced diastolic blood pressure.

At the recommended once-daily starting doses olmesartan medoxomil (20 mg), losartan (50 mg), valsartan (80 mg) or irbesartan (150 mg), the drug has shown to be the most effective in reducing diastolic blood pressure in patients with essential hypertension [34].

Pharmacokinetics

Olmesartan is an active metabolite of olmesartan medoxomil (prodrug). At a single oral dose, olmesartan medoxomil has (i) olmesartan peak plasma concentration (C_{max}) of 224 ng/ml at 10 mg dose and 2100 ng/ml at 160 mg dose (ii) time to reach C_{max} (T_{max}) of 1 - 3h, (iii) area under curve in time versus plasma concentration curve (AUC) of 1631 ng×h/ml at 10 mg dose and 19905 ng×h/ml at 160 mg dose (iv) elimination half-life (t½) of 10 - 15h, (v) a renal clearance of 0.43 - 0.92 L/h, independent of oral dose of 10 - 320 mg, (vii) > 99% bound to serum proteins, (viii) volume of distribution of 34.9 L at 20 mg dose, (ix) urine excretion of olmesartan medoxomil is about 35% to 50% while fecal excretion is 65 - 90% (x) Olmesartan is not metabolized by the cytochrome P-450 and has kidney and liver as dual route of elimination [35].

Clinical efficacy

Olmesartan medoxomil is very effective in the treatment of hypertension and as an anti-atherosclerotic agent [36,37].

Side effects

General side effects of olmesartan are hives, difficulty in breathing, swelling of faces, lips, tongue, throat. Serious side effects of olmesartan may include: dizziness, joint or muscle pain, back pain, stomach pain, nausea, diarrhea, mild itching or skin rash, or weakness. Severe side effects such as oliguria, chest pain, fast heart rate, swelling in hand [34].

Discussion

The renin-angiotensin system (RAS) has a vital role in the regulation of blood pressure, fluid-electrolyte balance and in the pathophysiology of various cardiovascular diseases. Although ACE inhibitors are generally well tolerated, their side effects, such as cough and angioedema, gave rise to the development of another way of blocking the RAS that has similar beneficial effects but with more efficacy and reduced risks of adverse effects. That another way of blocking the RAS is using antagonists of angiotensin II type 1

(AT1) receptors. The angiotensin II type 1 (AT1) receptors mediate almost all the major physiological actions of angiotensin II namely blood pressure regulation, aldosterone secretion and renal function, electrolyte and water balance [38]. In addition to their excellent tolerability and safety profile, angiotensin II receptor antagonists also have been proven to have protective properties in human organs, with beneficial effects on morbidity and mortality. Furthermore, in contrast to ACE inhibitors, angiotensin II receptor antagonists do not cause accumulation of vasodilatory and pro-inflammatory peptides (namely bradykinin and substance P), hence less likely to cause dry cough, exaggerated hypotension, and angioedema [39]. The efficacy of these angiotensin II receptor antagonists are generally comparable to or exceeds that of full doses of first line antihypertensive drugs such as ACE inhibitors, calcium channel blockers and thiazide diuretics.

Amongst the angiotensin II type 1 (AT1) receptor antagonists, candesartan has been found to be superior to losartan in reducing blood pressure and also causes fewer serious adverse events than losartan [40]. In patients with mild-to-moderate hypertension, irbesartan is to be more effective than losartan and valsartan (but not olmesartan), in terms of absolute reduction in blood pressure and response rate. Also, it is the drug of choice among angiotensin II type 1 (AT1) receptor antagonists in the treatment of diabetic neuropathy. Olmesartan, at its starting dose, is considered to be more effective than the starting doses of the other angiotensin II type 1 (AT1) receptor antagonists in reducing cuff diastolic blood pressure in patients with essential hypertension [41].

Conclusion

Hypertension treatment is very vital to prevent risks of developing chronic renal failure, heart failure, myocardial infarction, and stroke.

Angiotensin II receptor antagonists have comparable antihypertensive efficacy with first and second line antihypertensive drugs such as beta-blockers, diuretics (thiazides), calcium antagonists and angiotensin-converting enzyme (ACE) inhibitors but much better in tolerability and safety. Losartan and olmesartan have the lowest hepatic elimination, thus preferable to be used in cases of hepatic impairment. Eprosartan, telmisartan and valsartan have the lowest renal elimination, therefore better used in cases of renal impairment. Finally, the utility of angiotensin II receptor antagonists in controlling hypertension in clinical practice depends on their superiority over other antihypertensive agents in terms of (i) efficacy in the control of ambulatory, cuff diastolic and cuff systolic blood pressure (ii) patients tolerability (iii) safety profiles.

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Volume 5 Issue 9 September 2022