REVIEW ON AN ARB HAVING HIGHER ASSOCIATION LOWER DISSOCIATION INDEX FOR A RECEPTOR: A NEW TREND IN ACHIEVEMENT OF HYPERTENSION GOAL

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INTRODUCTION:
Hypertension is a known risk factor for cardiovascular events and mortality. It also doubles for every 20/10-mm Hg elevation beyond this level and at every age level. Seventh report of the Joint National Committee (JNC) on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure recommends a blood pressure (BP) goal of < 140/90 mm Hg for patients with uncomplicated hypertension and < 130/80 mm Hg for patients with type 2 diabetes mellitus (T2DM) or renal disease. Based on clinical evidence, patients with stage 1 hypertension (seated cuff systolic BP of 140–159 mm Hg or diastolic BP of 90–99 mm Hg) should be treated to targeted BP levels to reduce cardiovascular morbidity and mortality. Inadequate blood pressure (BP) control represents one of the major challenges of antihypertensive treatment, being responsible for the elevated cardiovascular morbidity and mortality associated with hypertension.
Numerous antihypertensive drugs, from a variety of pharmacologic classes and with different mechanisms of action, have been shown in randomized controlled trials to reduce cardiovascular morbidity and mortality, and it can be concluded that it is blood pressure reduction, and not some other pharmacologic property of the drugs, that is largely responsible for those benefits. The largest and most consistent cardiovascular outcome benefit has been a reduction in the risk of stroke, but reductions in myocardial infarction and cardiovascular mortality also have been seen regularly.
Elevated systolic or diastolic pressure causes increased cardiovascular risk, and the absolute risk increase per mmHg is greater at higher blood pressures, so that even modest reductions of severe hypertension can provide substantial benefit. Relative risk reduction from blood pressure reduction is similar across populations with varying absolute risk, so the absolute benefit is greater in patients who are at higher risk independent of their hypertension (for example, patients with diabetes or hyperlipidemia), and such patients would be expected to benefit from more aggressive treatment to a lower blood pressure goal.

PHARMACOLOGY:
Angiotensin II is the primary vasoactive hormone of the renin–angiotensin system and plays an important role in the pathophysiology of several chronic disease states. It is found in a variety of tissues and formed primarily from the conversion of angiotensin I to angiotensin II, a reaction

ABSTRACT
OLMESARTAN medoxomil (angiotensin II receptor blockers (ARBs) having blood pressure lowering efficacy similar to other antihypertensive agents. Recent large-scale, randomized, controlled clinical trials have demonstrated that ARBs offer cardiovascular and renal protective benefits independent of their effects on systemic blood pressure (BP), which make them valuable as first-line antihypertensive agents, especially in high-risk patients. However, as is the case with other antihypertensive classes, monotherapy with the first-available ARBs may not provide sufficient BP reduction to achieve currently recommended BP goals in many patients. The angiotensin II receptor blockers (ARBs) are well tolerated and demonstrate significant BP reduction. Olmesartan medoxomil, an ARB, has been well studied and achieves significant BP lowering and goal achievement with good tolerability. Olmesartan medoxomil is the latest angiotensin II receptor include once-daily dosing, an absence of significant adverse reactions, a well-tolerated side-effect profile, and a cost-effective average wholesale price. Olmesartan medoxomil is currently being used as an alternative therapeutic antihypertensive agent for patients intolerant of angiotensin-converting enzyme inhibitors (ACEIs).

Keywords: Olmesartan medoxomil, Randomized, Losartan, Valsartan, ACEIs, ARBs
catalyzed by ACE. To a lesser degree, human chymase and other non-ACE pathways also generate angiotensin II. Once synthesized, angiotensin II produces its biological effects by binding to either the angiotensin II–AT1 or AT2 receptor subtype. The AT1 receptor is found in brain, renal, myocardial, vascular, and adrenal tissue. Angiotensin II–AT2 receptors are located in the adrenal medullary tissue, uterus, and brain. AT1 receptors mediate the majority of responses crucial to cardiovascular and renal function. Less is known about the role of AT2 receptors; however, when these receptors are stimulated, they can cause vasodilation and can decrease endothelium proliferation. Like all ARBs, Olmesartan medoxomil exerts its pharmacological actions by selectively blocking angiotensinII–AT1 receptor sites in the vascular smooth muscle, thus inhibiting the vasoconstrictor effects of angiotensin II. One notable variation is the degree of binding to the AT1 receptor compared with the AT2 receptor; Olmesartan medoxomil exhibits more than a 12,500-fold greater affinity for the AT1 receptor than for the AT2 receptor, making it theoretically the second most potent agent. The order of binding affinity to the AT1 receptor, compared with the AT2 receptor, for the ARBs appears to be as follows: valsartan > Olmesartan medoxomil > candesartan > irbesartan > telmisartan > losartan > eprosartan. Because of a lack of head-to-head clinical trials, it is uncertain whether this order indicates differences in clinical efficacy.

PHARMACOKINETICS:

Olmesartan medoxomil, which is administered as a prodrug, is rapidly and completely de-esterified to the active metabolite Olmesartan (RNH-6270) during absorption from the gastrointestinal tract. Following the conversion of Olmesartan medoxomil to Olmesartan, virtually no further metabolism occurs. The bioavailability of Olmesartan is approximately 26%, similar to that of losartan and valsartan. Following oral administration, the peak plasma concentration (Cmax) of Olmesartan is reached after one to two hours. The bioavailability of Olmesartan is not affected by food. Olmesartan is eliminated in a biphasic manner, with a terminal elimination half-life of approximately 13 hours. It is highly bound to plasma proteins (99%) and does not penetrate red blood cells. Olmesartan takes approximately three to five days to reach a steady state, and there is no accumulation in plasma with once-daily dosing.

DRUG INTERACTIONS:

No significant drug interactions were reported in studies in which Olmesartan medoxomil was coadministered with digoxin or warfarin in healthy volunteers. The bioavailability of Olmesartan was not significantly altered by the co-administration of antacids [Al(OH)3/Mg(OH)2]. Olmesartan medoxomil is not metabolized by the cytochrome P450 system and has no effects on P450 enzymes; thus, interactions with drugs that inhibit, induce, or are metabolized by those enzymes are not expected.

Non-Steroidal Anti-Inflammatory Agents including Selective Cyclooxygenase-2 Inhibitors (COX-2 Inhibitors):

In patients who are elderly, volume-depleted (including those on diuretic therapy), or with compromised renal function, co-administration of NSAIDs, including selective COX-2 inhibitors, with angiotensin II receptor antagonists, including Olmesartan medoxomil, may result in deterioration of renal function, including possible acute renal failure.

Dual Blockade of the Renin-Angiotensin System (RAS):

Dual blockade of the RAS with angiotensin receptor blockers, ACE inhibitors, or aliskiren is associated with increased risks of hypotension, hyperkalemia, and changes in renal function (including acute renal failure) compared to monotherapy.

Colestevam hydrochloride:

Concurrent administration of bile acid sequestrating agent colestevam hydrochloride reduces the systemic exposure and peak plasma concentration of Olmesartan. Administration of Olmesartan at least 4 hours prior to colestevam hydrochloride decreased the drug interaction effect.

USE IN SPECIFIC POPULATION:

Pregnancy Category D:

Use of drugs that act on the renin-angiotensin system during the second and third trimesters of pregnancy reduces fetal renal function and increases fetal and neonatal morbidity and death. Resulting oligohydramnios can be associated with fetal lung hypoplasia and skeletal deformations. Potential neonatal adverse effects include skull hypoplasia, anuria, hypotension, renal failure, and death. When pregnancy is detected, discontinue Olmesartan medoxomil as soon as possible. If oligohydramnios is observed, discontinue Olmesartan medoxomil, unless it is considered lifesaving for the mother. Fetal testing may be appropriate, based on the week of pregnancy.
Nursing Mothers:  
It is not known whether Olmesartan is excreted in human milk, but Olmesartan is secreted at low concentration in the milk of lactating rats.

Pediatric Use:  
Neonates with a history of in utero exposure to Olmesartan medoxomil: If oliguria or hypotension occurs, direct attention toward support of blood pressure and renal perfusion. Exchange transfusions or dialysis may be required as a means of reversing hypotension and/or substituting for disordered renal function.

Geriatric Use:  
Of the total number of hypertensive patients receiving Olmesartan medoxomil in clinical studies, more than 20% were 65 years of age and over, while more than 5% were 75 years of age and older. No overall differences in effectiveness or safety were observed between elderly patients and younger patients.

Hepatic Impairment:  
Increases in AUC∞ and Cmax were observed in patients with moderate hepatic impairment compared to those in matched controls, with an increase in AUC of about 60%. No initial dosage adjustment is recommended for patients with moderate to marked hepatic dysfunction.

Renal Impairment:  
Patients with renal insufficiency have elevated serum concentrations of Olmesartan compared to subjects with normal renal function. After repeated dosing, the AUC was approximately tripled in patients with severe renal impairment (creatinine clearance < 20 mL/min). No initial dosage adjustment is recommended for patients with moderate to marked renal impairment (creatinine clearance < 40 mL/min).

Black Patients:  
The antihypertensive effect of Olmesartan medoxomil was smaller in black patients (usually a low-renin population), as has been seen with ACE inhibitors, beta-blockers and other angiotensin receptor blockers.

CLINICAL EFFICACY:

(1) Article from American society of hypertension (ASH) update 2013  
(a) Treatment of hypertension in elderly patients  
A protocol treatment with Nebivolol+Olmesartan+Furosemide+Ranolazine+Antiplatelet+Antidiabetes was successful in controlling BP and reducing other CV events in the elderly patients.

(b) Effect of Olmesartan and amlodipine over perindopril and amlodipine in reducing central aortic blood pressure  
The outcome of the trial was the superiority of the Olmesartan and Amlodipine combination in controlling CABP.

(2) Article from European society of Hypertension (ESH) 2013  
(a) Effect of Olmesartan along with Amlodipine on arterial stiffness in patients with hypertension  
Olmesartan along with amlodipine, effectively decreases the carterial stiffness.

(b) Efficacy of Olmesartan/Amlodipine medoxomil based regimen in elderly and non-elderly subjects with hypertension and type 2 diabetes mellitus - a comparative study  
AML/OM based titrations regimen is effective in lowering ABP and SeBP in elderly and non-elderly patients, which enabled the majority of them to achieve 24-hour BP control, and the drug was well tolerated by both groups.

(c) Impact of 30 or 90 days supply of Olmesartan on Patients adherence.  
Pateints with 90-days of Olmesartan medoxomil alone or in combination with HCTZ or amlodipine were found to have greater mean PDC, higher likelihood of achieving high adherence and lower rates of drug discontinuation than patients initially prescribed 30-days drug supply.

(d) Use of fixed dose triple drug therapy, Olmesartan, Amlodipine, HCTZ as replacement therapy for patients not at goal blood pressure – a comparative study.  
Starting of Olmesartan/Amlodipine/HCTZ therapy all patients achieved their office and ABPM BP goal, by ABPM measure post first dose.

(3) The Randomized Olmesartan and Diabetes Microalbuminuria Prevention (ROADMAP)  
The primary outcome was the time to the first onset of microalbuminuria. Olmesartan was associated with a delayed onset of microalbuminuria. The higher rate of fatal cardiovascular events with Olmesartan among patients with pre-existing coronary heart disease is of concern.

(4) Effect of High-dose Angiotensin II Receptor Blocker (ARB) Monotherapy versus ARB plus Calcium Channel Blocker Combination on Cardiovascular Events in Japanese Elderly High-risk Hypertensive Patients (OSCAR): a Randomized Trial  
The OSCAR study, first large clinical trial to investigate the efficacy of high-dose ARB vs. ARB plus CCB in high-risk elderly hypertensive patients, did not show any differences in reducing CV events/all cause death.
ARB plus CCB was superior in reducing CV events/all cause death in subgroup of patients with CV disease. High-dose ARB seemed to prevent CV events/all cause death in patients with diabetes alone in spite of the weakness in antihypertensive effect. Further study is needed.

(5) As Per circulation, Journal of AHA

**Antinflammatory Effects of Angiotensin II Subtype 1 Receptor Blockade in Hypertensive Patients With Microinflammation**

In conclusion, treatment with the Ang II receptor antagonist Olmesartan significantly reduces biochemical markers of (vascular) inflammation in patients with essential hypertension by as early as week 6 of therapy. These anti-inflammatory properties of Ang II receptor antagonists may have beneficial cardiovascular effects in addition to their blood pressure lowering action.

(6) From British Journal of Cardiology

**A Review of Olmesartan Medoxomil -- A New Angiotensin II Receptor Blocker**

ARBs have been proven in large, randomised, double-blind, placebo-controlled and comparative studies to be safe, well tolerated and effective in treating hypertension and heart failure. Olmesartan medoxomil is the newest member of the selective AT1R blocker family. It is an effective antihypertensive agent, consistently resulting in double figure reductions in mean systolic and diastolic blood pressure which are maintained over a 24-hour period with once-daily dosage. In addition to this, it has a good oral bioavailability, is not metabolised by the cytochrome P450 enzyme pathway, has a high affinity for the AT1R, is competitively priced and well tolerated. As yet, no trials have been performed to assess its impact on cardiovascular morbidity or mortality end points; however, these types of studies have been completed for other ARBs and the benefits are likely to be a class effect. With the recent publication of the AB:CD protocol[27] for the treatment of hypertension, and the increasing prevalence of this condition in the under 55s, the use of ARBs as first-line anti-hypertensive agents is likely to increase. Olmesartan medoxomil seems to be an effective first-line agent for this purpose.

(7) Olmesartan Medoxomil versus Atenolol

(a) The Van Mieghem Study

There was a small but significantly greater reduction in systolic BP from the baseline with Olmesartan medoxomil (−20.7 ± 1.0) than with atenolol (−17.2 ± 1.0).

(b) The Püchler Study

Mean reductions in systolic BP and diastolic BP from the baseline were similar for the Olmesartan medoxomil group (−20.4 ± 10.5/−17.3 ± 6.3 mmHg) and the atenolol group (−19.6 ± 10.5/−17.2 ± 6.4 mm Hg).

(8) Olmesartan Medoxomil versus Captopril

(a) The Williams Study

The reduction in the seated trough diastolic BP from the baseline was greater in the Olmesartan medoxomil group.

(9) Olmesartan Medoxomil versus Other Angiotensin II Receptor Blockers

(a) The Ball Study

The reduction in mean the seated systolic BP was greater in the Olmesartan group than in the losartan group (−14.9 ± 1.0 vs. −11.6 ± 1.0 mmHg);

(b) The Oparil Study

At week eight, the mean 24-hour ambulatory systolic BP was reduced significantly more with Olmesartan medoxomil (−12.5 mm Hg) than with losartan and valsartan (−9.0 and −8.1 mm Hg; P < .05) but not more than with irbesartan (−11.3 mmHg).

(10) Comparison of Effects of Olmesartan and Telmisartan on Blood Pressure and Metabolic Parameters in Japanese Early-Stage Type-2 Diabetics with Hypertension

In conclusion, at clinical doses in patients with type-2 diabetes, Olmesartan seems to have more potent blood pressure lowering and anti-inflammatory effects than telmisartan, but similar effects on metabolic parameters. Our results suggest that Olmesartan can be considered an ideal agent to prevent future onset of cardiovascular disease in type-2 diabetic patients with hypertension.

**CONCLUSION:**

Olmesartan medoxomil is the newest angiotensin II receptor blocker approved for the treatment of hypertension. It is well tolerated, with an adverse effect profile similar to that of placebo, except for the incidence of dizziness (which is greater with Olmesartan medoxomil), and is devoid of any significant drug interactions. The drug provides smooth 24-hour BP control with once daily dosing, and comparative studies suggest that it might have a equal efficacy to atenolol and greater efficacy than captopril, losartan, valsartan, and irbesartan. Currently, Olmesartan medoxomil has a place in therapy as an alternative antihypertensive agent for patients intolerant of ACE inhibitors. However, because the ACE inhibitors as well as some ARBs are also indicated for the treatment of heart failure, left ventricular dysfunction after myocardial infarction, and/or proteinuria, further studies are warranted to establish Olmesartan medoxomil as a cardiovascular or renal protective agent. Olmesartan associated with Prevention of Microalbuminuria in Type 2 Diabetes.

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2. ASH update 2013.


