The Use of Drugs Affecting the Renin Angiotensin System in the Management of Hypertension

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Introduction

The Renin Angiotensin System (RAS) plays a significant role in the pathophysiology of a variety of disease states including hypertension, heart failure, myocardial infarction, and nephropathy.[1] Until recently, the Angiotensin Converting Enzyme (ACE) Inhibitors and Angiotensin Receptor Antagonists or Blockers (ARBs) were the only approved drug classes directly affecting the RAS. On March 5, 2007 the FDA approved aliskiren, an oral antihypertensive agent in a new class of drugs also affecting the RAS. This new class is referred to as the direct renin inhibitors and they are the newest antihypertensive class to be approved within the past ten years.

Pharmacology

In order to understand the pharmacology of these drug classes, it is important to understand how the RAS works (page 17 figure). Renin is a circulating enzyme which is synthesized, stored, and released by juxtaglomerular cells in the kidney. Renin is the enzyme responsible for catalyzing the rate limiting step of the RAS pathway. Angiotensinogen, a substrate of renin, is cleaved into angiotensin (Ang) I. The next step in the pathway occurs when angiotensin converting enzyme cleaves Ang I into Ang II. Ang II increases total peripheral resistance by acting as a direct vasoconstrictor and has an effect on myocardial hypertrophy and remodeling. Additionally, Ang II affects renal function through its effects on sodium reabsorption, aldosterone release, and decreasing renal blood flow. These actions occur when Ang II binds to either the angiotensin type one (AT_1) receptor or the angiotensin type two (AT_2) receptor. Most effects of angiotensin are due to the binding of angiotensin to the AT_1 receptor. The AT_2 receptor is generally considered cardioprotective; however, its functional role has so far been poorly defined.[1] Renin inhibitors directly influence the rate limiting step of the RAS; however, both ACE inhibitors and ARBs act during later stages of the pathway. The ACE inhibitors interrupt the RAS by competitively inhibiting ACE which leads to decreased production of Ang II. While this causes some of the antihypertensive effects seen with ACE inhibitors, it is not the only mechanism. Additional benefits may be due to the increase in bradykinin levels. ACE is structurally identical to kinase II which inactivates kinins; therefore, inhibiting ACE potentiates kinin activity (e.g., bradykinin) which may lead to further blood pressure lowering effects through bradykinin's ability to cause vasodilation.[2,3] The ARBs have similar effects to the ACE inhibitors, but exhibit their effect even later in the pathway. Instead of inhibiting an enzyme, they competitively bind to the AT_1 receptor, thus inhibiting most biological effects of Ang II. Although ACE inhibitors have the potential to reduce the effect of Ang II on the AT_1 and AT_2 receptors, it is the

ARBs which mainly lower blood pressure by binding directly to the AT_1 receptor. The production of Ang II may be catalyzed by enzymes other than ACE that are present in the heart and possibly other areas of the body. For example, chymase, a serine protease, has been associated with ACE independent production of Ang II in human arteries.[4] ARBs can inhibit the effect of the Ang II produced through this pathway where the ACE inhibitors can not.

Antihypertensive Response

In the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), approximately 1,800 (61% of participants) hypertensive patients 55 years or older with one or more risk factors for coronary heart disease treated with the ACE inhibitor lisinopril for five years reached their blood pressure goal of < 140/90 ($P<0.001$).[5] Data has shown that ACE inhibitors appear to be less effective in black patients when compared to their use in Caucasians. According to Materson et al, the response rates in black patients over the age of sixty taking the calcium channel blocker diltiazem or hydrochlorthiazide were higher than those taking the ACE inhibitor captopril.[6] As part of the ALLHAT study, high risk hypertensive patients were randomly assigned to the calcium channel blocker amlodipine or the ACE inhibitor lisinopril. In this study, black patients responded better to amlodipine than lisinopril.[7] Despite ACE inhibitor monotherapy having a poor response in black patients, the addition of a thiazide diuretic leads to blood pressure lowering effects similar to that seen in Caucasian patients.[8]

In a small study comparing efficacy and tolerability of the ARB losartan versus atenolol in patients with mild to moderate hypertension, losartan lowered systolic blood pressure (SBP) 11.4 mmHg after twelve weeks of treatment and diastolic blood pressure (DBP) 8.6 mmHg. There was no significant difference between atenolol and losartan blood pressure lowering effects.[9] In the Losartan Intervention For Endpoint reduction in hypertension study (LIFE), losartan was compared to the beta blocker atenolol in order to evaluate both morbidity and mortality in patients with hypertension and left ventricular hypertrophy. Approximately 9,000 patients were monitored in this randomized, double blind study. In this study, patients taking atenolol encountered a mean SBP lowering effect of 29.1 mmHg and patients in the losartan group had a mean SBP lowering effect of 30.2 mmHg. Despite this comparable decrease in blood pressure, patients in the losartan group experienced less cardiovascular mortality, myocardial infarction, and stroke ($p=0.021$).[10] In a study comparing the efficacy of olmesartan, losartan, valsartan, and irbesartan, researchers reported a 24-hour systolic blood pressure decrease of 8.1-12.5 mmHg and a diastolic decrease of 5.6-8.5 mmHg with olmesartan having the greatest effect, followed (in order) by irbesartan, losartan and valsartan.[11] Newer members of the ARB class, for example candesartan, telmisartan, and olmesartan, may be more effective in controlling hypertension than valsartan and other older agents.

A study published in 2005 reported alsikerin 150 mg to be as effective as 150 mg of the ARB, irbesartan, in patients with mild to moderate essential hypertension.[12] In a review article comparing five trials evaluating aliskiren monotherapy, systolic blood pressure decreases ranged from 8 mmHg to 15.8 mmHg and diastolic blood pressure decreases ranged from 4.5 mmHg to 11.8 mmHg.[13] This is similar to decreases in blood pressure seen with both ACE inhibitors and ARBs.

Adverse Effects and Contraindications

Adverse effects exhibited by ACE inhibitors, ARBs, and renin inhibitors are typically caused by the blockade of the RAS system. With ACE inhibitors, the increase in bradykinin also plays an important role in adverse effects. All drugs acting on the RAS pathway have a black box warning stating injury and death may occur to the developing fetus when used in the second and third trimesters.[14] Hypotension is a possible adverse effect with each of these drugs, but is usually only a concern in patients with heart failure or who are volume depleted. Hyperkalemia is also possible with all three of the RAS drug classes and is mainly due to the decrease in aldosterone concentrations, which plays a role in the urinary excretion of potassium. Other factors which can lead to hyperkalemia are dietary potassium intake (sometimes due to the use of potassium containing salt substitutes), other medical conditions, as well as, drug-drug interactions. Medical conditions increasing the chances of experiencing hyperkalemia include renal impairment and hypoaldosteronism. Concurrent use of either ACE inhibitors, ARBs, or renin inhibitors with the following drugs can also contribute to worsening hyperkalemia: NSAIDs, COX-2 inhibitors, immunosuppressants, and potassium sparing diuretics.[15] A decrease in Ang II has been associated with a decline in glomerular filtration rate (GFR) which can lead to a decline in renal function in some patients. [16] Because of this, patients' renal function should be monitored after initiation with one of these drugs. Both ACE inhibitors and ARBs are contraindicated in patients with bilateral renal artery stenosis. Renal artery stenosis (RAS) can lead to renal ischemia due to decreased afferent artery blood flow. In patients with RAS, GFR is maintained through vasoconstriction caused by Ang II. By blocking this Ang II-mediated vasoconstriction, decreased GFR will result.[17] Adverse effects of ACE inhibitors include dry cough and angioedema, occurring as a result of an increase in bradykinin. A dry cough develops in about 5 to 20% of patients taking an ACE inhibitor and is more commonly seen in women patients. Although angioneurotic edema (angioedema) only occurs in 0.1% to 0.2% of patients taking ACE inhibitors, it can be a life threatening adverse effect of these drugs.[18] Even though bradykinin levels are not increased with the use of ARBs or renin inhibitors, several cases of both cough and angioedema have been reported. A history of angioedema is a contraindication to the use of both ACE inhibitors and ARBs. Although aliskiren has no listed contraindications, it should be used cautiously in patients with a history of angioedema since its effects on bradykinin are currently unknown. The most common adverse effects reported with alsikerin use are headache, dizziness and diarrhea. These effects appear to be dose related.[15]

Conclusion

ACE inhibitors and ARBs are currently recommended for their blood pressure lowering effects in patients with Stage I and Stage II hypertension, especially for those with compelling indications such as diabetes, heart failure, coronary artery disease, and chronic kidney disease.[19] Although aliskiren appears to have less side effects associated with it and similar blood pressure lowering effects to the ACE inhibitors and ARBs, its place in therapy is currently undefined. No available data on long term morbidity or mortality effects with aliskiren exists at this time; however, there are currently several phase III trials assessing aliskiren's effect on diabetic nephropathy, heart failure, and left ventricular hypertrophy. Perhaps when the data from these trials are released, clinicians will have a better idea whether or not renin inhibitors should also be considered a preferred antihypertensive agent when considering a drug that can lower blood pressure, as well as, prevent end organ damage.

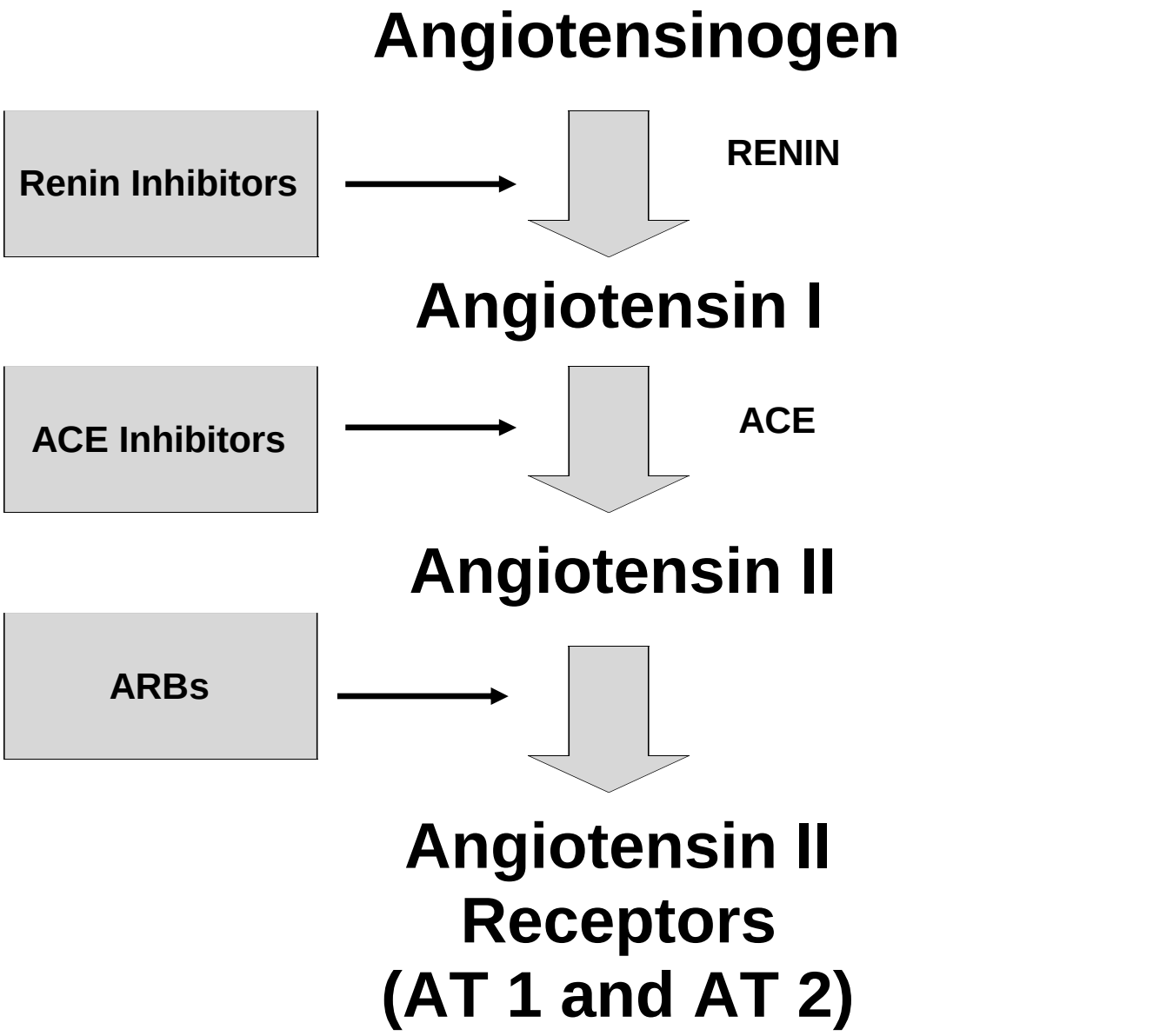
Angiotensinogen
Renin Inhibitors
RENIN
Angiotensin I
ACE Inhibitors
ACE
Angiotensin II
ARBs
Angiotensin II Receptors (AT 1 and AT 2)

Table 1: ACE Inhibitors Available in the United States [20]

Generic Name	Trade Name	Available Strengths (mg)	Usual Adult Maintenance Dose	Generic Available
Benazepril	Lotensin®	5, 10, 20, 40	20-40 mg in 1-2 divided doses	Yes
Captopril	Capoten®	12.5, 25, 50, 100	12.5-150 mg 2-3 times per day	Yes
Enalapril	Vasotec®	2.5, 5, 10, 20	5-40 mg in 1-2 divided doses	Yes
Fosinopril	Monopril®	10, 20, 40	20-40 mg in 1-2 divided doses	Yes
Lisinopril	Prinivil®/Zestril®	2.5, 5, 10, 20, 30, 40	10-40 mg in 1-2 divided doses	Yes
Moexipril	Univasc®	7.5, 15	7.5-30 mg in 1-2 divided doses	No
Perindopril	Aceon®	2, 4, 8	4-16 mg in 1-2 divided doses	No
Quinapril	Accupril®	5, 10, 20, 40	10-40 mg once daily	Yes
Ramipril	Altace®	1.25, 2.5, 5, 10	2.5-5 mg once daily	No
Trandolapril	Mavik®	1, 2, 4	1-4 mg once daily	Yes

Table 2: ARBs Available in the United States [21]

Generic Name	Trade Name (manufacturer)	Available Strengths (mg)	Usual Adult Maintenance Dose	Generic Available
Candesartan	Atacand®	4, 8, 16, 32	4-32 mg once daily	No
Eprosartan	Teveten®	400, 600	400-800 mg in 1-2 divided doses	No
Irbesartan	Avapro®	75, 150, 300	150-300 mg once daily	No
Losartan	Cozaar®	25, 50, 100	50-100 mg in 1-2 divided doses	No
Olmesartan	Benicar®	5, 20, 40	20-40 mg once daily	No
Telmisartan	Micardis®	20, 40, 80	20-80 mg once daily	No
Valsartan	Diovan®	40, 80, 160, 320	80-320 mg once daily	No

Table 3: Direct Renin Inhibitor Available in the United States[14]

Generic Name	Trade Name (manufacturer)	Available Strengths (mg)	Usual Adult Maintenance Dose	Generic Available
Aliskiren	Tekturna®	150, 300	150-300 mg daily	No

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