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Scientific Update™

New pharmacologic approaches to the management of hypertension

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Angiotensin-II antagonists represent a new therapy in the management of hypertension as well as intervention with respect to physiologic and structural changes related to this disease. Through the blockage of angiotensin-II type 1 receptors, there is an opportunity for complete inhibition of renin-angiotensin system (RAS) activation. Moreover, the increase in efficacy in relation to increasing the dose of these medications, is associated with an excellent safety profile, including a frequency of side effects similar to that of placebo across a wide range of doses.

Hypertension: burden of disease

Hypertension and related co-morbid conditions continue to contribute significantly to the overall morbidity and mortality related to cardiovascular disorders. The World Health Organization's global burden of disease study revealed that hypertension, along with tobacco and malnutrition, is one of the three top contributors to overall mortality worldwide. While prevalence of coronary heart disease and stroke has decreased from 1970-1990, this trend has flattened since 1990, suggesting that newer approaches are required for further management of this disorder.

Importantly, the presence of hypertension alone is not the only risk factor for increased morbidity and mortality. Other co-morbid conditions, such as hyperinsulinemia and insulin resistance, obesity, dyslipidemia, left ventricular hypertrophy (LVH), and an increase in platelet reactivity or hematocrit are important modulators of the overall disease burden. While a number of antihypertensive medications may have a similar efficacy in lowering blood pressure (BP), treatments may differ widely in their effects on other metabolic factors. For example, the Tecumseh BP Study revealed that, for the same antihypertensive effect, beta-blockers decreased insulin sensitivity, while ACE inhibitors and other vasodilators improved it.[1]

Thus, control of hypertension should be seen in the setting of an overall approach that addresses functional and structural abnormalities. For example, LVH is an important and obvious manifestation of end-organ damage that results from trophic changes influenced by factors such as increased levels of plasma norepinephrine, plasma renin, and angiotensin II — all of which are elevated in hypertension. Prevention of LVH, which has been strongly correlated with 5-year mortality from Framingham study, should be an important goal of antihypertensive treatment.

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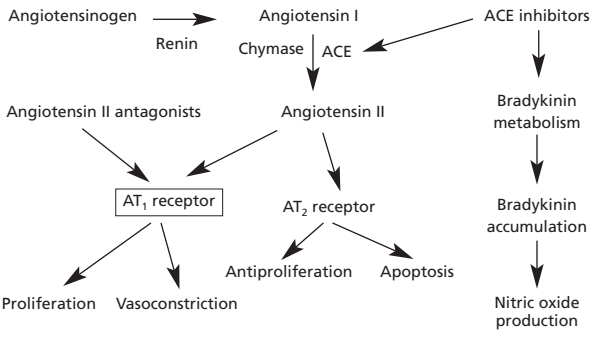
Control, rather than treatment of hypertension, should be the goal. Even with current awareness of the importance of antihypertensive treatment, <60% of patients are controlled, based on recommended cut-off levels: systolic blood pressure of 140 mm Hg and diastolic blood pressure of 90 mm Hg. There is a tendency for physicians to focus on significantly or severely hypertensive patients and take a less aggressive approach in patients who are mildly hypertensive. Yet, more than 50% of the overall mortality related to hypertension occurs in mildly hypertensive patients.

Development of new antihypertensive treatment

The importance behind the development of angiotensin-II antagonists has been completeness and specificity in blockade of the renin-angiotensin system, resulting in improved antihypertensive efficacy and less frequent adverse effects.

Figure 1: Angiotensin II-receptor antagonists



As seen in Figure 1, production of angiotensin II may occur via activity of angiotensin-converting enzyme (ACE) and through the chymase pathway, which is not inhibited by ACE inhibitors. Chymase is a serum proteinase with a high affinity for angiotensin I. While its production is not significant in a normal heart, increases in production have been observed in the setting of heart failure and after myocardial infarction and in patients with restenosis after PTCA.

While the physiological and clinical importance of the chymase pathway has not been determined or elucidated, results of the ELITE I study demonstrated a significant reduction in all-cause mortality with losartan by comparison to captopril (4.8% vs 8.7%). This data suggests that complete and targeted inhibition of angiotensin II effects may be more beneficial than the less specific inhibition achieved with ACE inhibitors.

Angiotensin-II receptor blockade

At least two angiotensin (AT)-II receptors have been described. AT_1 receptor is known to be involved with BP control and volume homeostasis. Its activation is known to affect vasoconstriction in the vascular tree, inotropy in myocardium, sodium reabsorption and renin inhibition in the kidneys, and aldosterone and vasopressin secretion in renal medullae and pituitary, respectively. Thus, blockade of this receptor by angiotensin-II antagonists inhibits the pressor response and lowers BP. Other beneficial effects, similar to those observed with ACE inhibitors, have been demonstrated in animal models, including regression of LVH and ventricular remodeling, improvement in morbidity and mortality, and protection against renal damage in diabetic nephropathy.

As with ACE inhibitors, administration of angiotensin-II antagonists results in increases in renin and angiotensin II levels, which may lead to an unopposed effect on AT_2 receptors.

Angiotensin-II antagonists are not known to exert a significant effect on AT_2 receptors. AT_2 receptors are mostly expressed in embryo with some expression in the adrenal medulla. They are thought to participate in the regulation of growth, myocardial and vascular healing post injury, antiproliferation, and apoptosis.

Pharmacokinetics of angiotensin-II antagonists

A number of angiotensin-II antagonists are in various stages of development, including losartan, irbesartan, valsartan, candesartan, eprosartan and tasosartan. The bioavailability and plasma half-life varies significantly among these compounds; the greatest bioavailability of about 60-80% and the longest half-life of about 11-15 hours is seen with irbesartan. Most angiotensin-II antagonists, except irbesartan, are metabolized to a more active compound. For example, losartan is metabolized to EXP 3174, which has longer half-life and more powerful anti-

hypertensive effect than the parent compound. EXP 3174 has a greater affinity for AT_1 as compared to losartan. Irbesartan has a similarly high affinity for the AT_1 receptor.

Clinical overview of irbesartan

No clear or significant body of knowledge exists with respect to comparison of various angiotensin-II antagonists.

Losartan is the only angiotensin-II inhibitor that has been shown to reduce mortality in patients with heart failure (ELITE I study).[2] A larger ELITE II study is planned to confirm these results. While similar data are not available for other agents, these drugs are believed to have a class effect, although comparative studies are not available. All angiotensin-II antagonists share an excellent side-effect profile with no known significant side effects. Irbesartan appears to have an excellent pharmacodynamic profile with a dependable and predictable relationship between plasma concentration and administered dose as well as a dose-related BP reduction.

Once-daily administration of irbesartan has been demonstrated to lead to a significant and sustained reduction in BP based on observations from ambulatory BP monitoring. Normalization of BP is seen in a dose-dependent fashion, ranging from 20-60% as the dose is increased from 75-500 mg with a dose-related lowering in diastolic BP of between 4-10 mm Hg. The rate of BP normalization with 150-300 mg of irbesartan has been shown to be similar to that of 20-40 mg of enalapril and 50-100 mg of atenolol. Observations of the dose-response curve suggest some flattening of response beyond 150 mg, suggesting that this may be an optimal starting or maintenance dose. However, for more severe hypertension, the response, though not linear, is significant with the 300 mg dose. Adequate control of BP with irbesartan doses of up to 300 mg was observed in up to 74% of patients with monotherapy; the remaining 26% required additional therapy.

Overall clinical experience with irbesartan suggests efficacy in treatment of hypertension through significant, near-complete inhibition of the renin-angiotensin system with a substantiative effect after 1-2 weeks of therapy. There appears to be a clear dose-response relationship with a sustained BP response over 24 hours. Comparable efficacy to other antihypertensive treatments, across various age groups and in both genders, has also been noted. As is the case with ACE inhibitors, irbesartan and other angiotensin-II antagonists appear to be less effective in African-Americans. This lower efficacy can be potentiated through further activation of renin-angiotensin system with the addition of low-dose hydrochlorothiazide. It should also be noted that the efficacy of angiotensin-II antagonists increases significantly with salt depletion, which may offer clinicians a simple way to increase the antihypertensive efficacy of these compounds.

Adverse effects of irbesartan and other angiotensin-II antagonists are low and similar to placebo including frequently observed side effects of cough, dizziness, fatigue, edema, and reduced sex drive. This low incidence of side effects is maintained when the dosage of irbesartan needs to be increased for more antihypertensive effect.

Renal protection in diabetic nephropathy

Diabetic nephropathy is a significant contributor to the overall disease burden and causes 35% of end-stage renal disease requiring dialysis. Up to 63% of patients with type II diabetes mellitus have evidence of diabetic nephropathy.

The initial stage of diabetic nephropathy is hyperfiltration. There is a significant increase in glomerular filtration rate by comparison to normal individuals and similar to that observed in obese individuals. Microalbuminuria is seen in 23-29% of patients with type II diabetes and represents an early and significant predictor of cardiovascular risk in these patients. There appears to be a correlation between BP control and renal damage in type II diabetics.

The benefits of BP control with ACE inhibitors have clearly been demonstrated in type I diabetic patients. A decrease in BP leads to a decrease in albuminuria and slows the progression of renal failure. Because angiotensin II is implicated in progressive renal disease, there is a suggestion that angiotensin-II antagonists may be as or perhaps even more effective than ACE inhibitors in renal protection by comparison to placebo, for example irbesartan has been shown to increase plasma renal flow.[3]

A recent, 14-week, double-blind, multicenter comparison of irbesartan (24 patients) and amlodipine (23 patients) observed a similar decrease in sitting diastolic BP. There appeared to be slight increases in proteinuria and albuminuria with amlodipine but a decrease with irbesartan. Furthermore, creatinine clearance increased with irbesartan but decreased with amlodipine.

These findings have led to the establishment of a collaborative study group, which will compare irbesartan, amlodipine, and placebo in a multicenter, randomized, double-blind study of 1,650 patients with type II diabetes mellitus in Europe, North America, and South America. Inclusion criteria will require evidence of nephropathy with proteinuria (≥ 1 gm/day), serum creatinine of ≤ 3.0 mg/dL (265 mmol/L), and history of hypertension. In addition to dietary recommendations and treatment with oral hypoglycemics or insulin, based on need, by attending physicians, the use of other antihypertensive medications will be allowed for the control of hypertension with a goal of systolic blood pressure < 135 mm Hg and diastolic blood pressure < 85 mm Hg. All patients will be followed for a minimum of 2 years with an expected average follow-up of 3 years. The primary end-point will be a composite end-point of: doubling of creatinine; end-stage renal disease requiring dialysis and death.

Summary

Angiotensin-II antagonists represent a significant advancement in antihypertensive therapy with complete and focused blockade of the renin-angiotensin system. Absence of side effects in the setting of sustained efficacy make angiotensin-II antagonists, such as irbesartan, significant additions to our armamentarium of antihypertensive therapy. Further studies are needed and are on the way to address clinical benefits of angiotensin-II antagonists, particularly in patient subpopulations who may benefit from angiotensin-II antagonists to a greater degree, and to define further need and rationale for combination therapy with an ACE inhibitor.

References

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Further references which have not yet been published are available upon request.