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Role of Angiotensin II Receptor Antagonists in Hipertensión

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Introduction

The first receptor antagonist of angiotensin II available for clinical use was Saralasin, a partial agonist, a peptide analogue of angiotensin II about 25 years. ago[1,2]. Saralasin was a agent used only intravenously for investigational purpose because was not orally active and with very short duration of action; further more increased blood pressure initially due to partial agonist effect; but prevented increment of blood pressure when angiotensin II was administrated.

Furukawa et al[3] was the first to synthesize an imidazole derivative that was found to be a selective angiotensin II receptor competitive antagonist, and after chemical modifications, orally active agent[4].

Losantan was the first orally active, and long acting receptor antagonist developed and in use in the treatment of hypertension[5,6], following by valsartan, irbesartan, eprosartan, candesartan, telmisartan and other[7].

Blockade of renin-angiotensin system is efficacious and safe way to reduce blood pressure and treatment of patients with hypertersion and heart failure, mainly by the inhibition of angiotensin converting enzyme, but some side effects are seen with this class of agents; such as, cough and angioedema in 5 to 10% of patients treated[8]. Angiotensin receptor antagonists have the advantage to have very low incidence of such side effects. However the place of this class of antihypertensive action remain to be defined.

Angiotensin II Receptors

Angiotensin II exerts its effects by stimulating some specific receptors on the membrane of several organs. Radioligand studies have characterized several angiotensin II receptors, mainly type I and type II (AT-1 and AT-2 receptor). Activation of AT-1 receptor leads to vasoconstriction, stimulation of the release of catecholamines and antidiuretic hormone and production of thirst; also promoting growth effects in vascular and cardiac muscle[9]; all those effects are blocked by AT-1 antagonists. Activation of AT-2 receptors tends to have opposite effects basically cardio protective effects by inhibitory effects on growth mechanisms at vascular and cardiac level.

AT-2 receptor are expressed during the intrauterine life but not during the adult life; however in pathological conditions; such as, myocardial infarction, left ventricular hypertrophy and in vascular neointimal proliferation the AT-2 receptor are re-expressed; in those conditions AT-2 receptor stimulation may produce a protection in heart and vessels. When AT-1 receptor antagonists block AT-1 receptors, actions of AT-1 receptors are inhibited but angiotensin II produce stimulation on AT-2 receptor [10].

Actions meditated by AT-1 and AT-2 receptors can be summarizing in table 1.

Other angiotensin II receptors have being described, such as, AT-3 ant AT-4[11]; also in rats and mice AT-1 receptor is composed of two subtypes: AT-1A and AT-1B[12]; those receptors have to be characterized pharmacologically and determinate its clinical relevance.

AT-1 Antagonists

The first chemically useful, orally active AT-1 receptor antagonist was losartan following by other agents nowadays, in clinical use or under investigation.

The table II summarizes the AT-1 receptor antagonist either in clinical use or under development:

The AT-1 receptor antagonists reduce blood pressure by decreasing systemic vascular resistance; heart rate and cardiac output are not modified[13,14,15]. Reduction in systemic vascular resistance are due to inhibition of the direct vasoconstrictive effect of angiotensin II; reductions in the sympathetic nervous system activity; in the release of aldosterone and in the reabsortion of sodium are mediated by angiotensin II. Also it has been described sensitizing in baroreceptors; stimulation of prostacyc1in release; and at long term reduction in the proliferative effect (antiproliferative effect)[7].

In volunteers the administration of AT-1 receptor antagonists increase plasma renin activity and angiotensin II levels either in acute administration or multiple dose administration[16,17]; but pressure effect of angiotensin II is blocked. On the contrary, ACE inhibitors reduce plasma level of angiotensin II and increase bradykinin levels.

The efficacy in reducing blood pressure with the use of AT-1 receptor antagonists is equivalent to other well establish antihypertensive agents. When compare losartan (50 to 100 mg daily) to felodipine (5 to 10 mg daily), losartan was less effective after 6 weeks of treatment but equally effective after 12 weeks of therapy[18].

The efficacy of losartan (50 to 100 mg once daily) has been compared to atenolol (50 to 100 mg once daily), and enalapril (20 mg once daily). The blood pressure lowering effect of losartan was comparable to enalapril and atenolol. On ambulatory blood pressure monitoring losartan showed antihypertensive effect during the 24 hours without affecting the body's circadian rhythm[19, 20].

Several studies have compared the blood pressure lowering effects of AT-1 receptor antagonist against enalapril; candesartan cilexitl[21]; eprosartan[22] and irbesartan[23] lower blood systolic and diastolic blood pressure to the same extends from that of enalapril.

When diuretics were added to an AT-1 receptor antagonist, a better response is achieved. So the addition of hydrochorothyazide to losartan produce a dose related reduction in blood pressure after a treatment of 12 weeks [19]. In a double blind study 189 patients were enrolled to compare valsartan + HCTZ (12.5 mg) and Enalapril + HCTZ (12.5 mg), after 8 weeks of treatment controlled blood pressure in about 64% of the patients in both group of treatments[24].

Losartan has been shown to exert a uricosuric effect in normotensive and hypertensive subjects; which could be an advantage when losartan is combined with a thiazide diuretic [20].

Effect on Left Ventricular Hypertrophy

Angiotensin Converting Inhibitors are particular effective in reducing and may be preventing left ventricular hypertrophy in hypertensive patients mediated by several mechanism; such as, reduction of circulating angiotensin II and aldosterone and increment of bradykinin[25,26]. Losartan and other AT-1 receptor antagonists reduce left ventricular hypertrophy in spontaneously

hypertensive rat[27]; even at dosage that does affect neither blood pressure nor the circulating rennin-angiotensin system but always in rats[28]. Thürmann PA et al,[29] in a double-blind randomized trial on 69 previous1y untreated hypertensive patients comparing valsartan (80 to 160 mg daily) to atenolol (50 to 100 mg daily) during 8 months found that valsartan reduced left ventricular mass index at higher extend than atenolol with similar reduction in systolic and diastolic blood pressure. Further documentation of the effects on left ventricular hypertrophy and long-term benefit and risk reduction has to be evaluated in other trials.

Pharmacokinetic

All AT-1 receptors antagonists studied to date seem to share essentially the same pharmacodynamic characteristics, but these agents differ in their pharmacokinetic characteristics in relationship to absorption, bioavailability, metabolism, elimination, duration of actions and half life.

Table III summarize the pharmacokinetics of some AT-1 receptor antagonists in clinical use. Only two agents have active metabolites: losartan and candesartan cilexitil, which contribute. to duration of action of those agents. Drugs with higher bioavailability are irbesartan and telmisartan; also those drugs have the longest half-life. All AT-1 antagonists are highly protein-bound.

Side Effects

AT-1 receptor antagonists are very well tolerated. The incidence of cough is similar to diuretics or placeb[31]. Dizziness, upper respiratory tract infection, back pain, sinusitis, diarrhea and pharyngitis have being reported to be 1 to 2% higher than placebo with different agents[32].

Chan P et al,[33] compared the incidence of cough with the ACE inhibitor lisinopril and the diuretic metolazone with losartan in elderly hypertensive patients with previous histories of ACE inhibitor induce cough, in a randomized, double blind, parallel group comparison of each drug during 10 weeks in 84 patients. The incidence of cough with losartan (18%) was significantly lower than lisinopril (97%) and similar to that for metolazone (2l%).

AT-1 receptors antagonists do not modify glucose tolerance neither cholesterol nor triglycerides levels.

Drugs that act directly on the rennin-angiotensin system can cause fetal and neonatal morbidity and death when administered to pregnant women, any of the AT-1 receptor antagonists should not be use during pregnancy and should be discontinued as soon as possible when pregnancy is detected.

Conclusions

AT-1 receptor antagonists are a new class of antihypertensive drugs, which are effective in reducing high blood pressure in hypertensive patients. In monotherapy in mild to moderate hypertensive patients control blood pressure in 40 to 50% of them; when a low dose of thiazide diuretic is added 60 to 70% are controlled. Blood pressure is reduced with equally efficacy compared to ACE-inhibitors, beta-blockers and calcium. channel blockers.

Tolerability has been reported to be excellent with the use of AT-1 receptor antagonists. Those drugs should be used in patients who has developed cough when using an ACE inhibitor.

The place in the antihypertensive therapy in special population and different clinical conditions; such as, lefl ventricular hypertrophy, associated heart failure, diabetes, and renal disease has to be determined in large clinical trial.

Table 1: Differences between AT1 and AT2 receptors

Angiotensin II AT1 receptor	**Angiotensin II AT2 receptor**
•Vasoconstricción	•Stimulation of Apoptosis
•Aldosterone production and release	•Antiproliferative effect
•Sodium tubular Reabsortion	•Embriogenic differentation and development
•Hypertrophy of heart	•Endothelial cells growing
•Proliferation of Smooth muscle in vascular tree	•Vasodilatación
•Catecholamines secretion and potentiation (central y periphery)	
•Vasopressin release	
•Thirst	
•Renal vasoconstriction and reduction Renal Blood Flow	
•Inhibition of renin release	

Table 2: Angiotensin II receptor antagonists

Agent	Established oral dose	Manufacturer
Losartan	50 - 100 mg daily	DuPond-Merck
Eprosartan	150 -350 mg daily	SmithKline Beecham
Irbesartan	10 - 50 mg daily	Sanofi
Telmisartan	40 - 80 mg daily	Boeringer Ingelheim
Candesartan	5 - 10 mg daily	Takeda - Astra
Valsartan	80 - 160 mg daily	Novartis
ZD-8731		Zeneca
SC-52458		Searle
LR-B/081		Lusofarmaco
YM-358		Yamanouchi
GR 117 289C Zolarsartan*		Glaxo

** Development suspended*

Table 3 : Summary of Pharmacokinetic Parameters of AT-1 receptor antagonists in clinical

Agent	Active Metabolite	Bioavailability (%)	Food Effect	Half Life (hours)	Protein bound (%)
Losartan	EXP-3174	33%	Minimal	6 - 9	98.7
Eprosartan	None	13%	Minimal	5 - 9	98
Irbesartan	None	60 - 80	None	11 - 15	90
Telmisartan	None	30 - 60	Minimal	24	> 98
Candesartan	Candesartan	15	None	9	> 90
Cliexetil					
Valsartan	None	25	Important	6	95

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