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Scientific Update™

Treatment of Hypertension: Past Achievements and Current Challenges

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Despite significant progress over the past two or three decades, arterial hypertension remains a worldwide public health problem of colossal proportions. It places third after malnutrition and smoking as a cause of global morbidity and mortality. Even in North America, and in Canada in particular, where the population has a high frequency of interactions with the health system on average, only a small minority of hypertensive patients — 16% in Canada — is adequately controlled. A better understanding of the pathophysiology of hypertension, as well as more effective and better-tolerated drugs, are needed if this epidemic and its often devastating consequences are to be brought under control.

The renin-angiotensin system (RAS) plays a crucial role in hypertension and its impact on target-organ damage. The first generation of agents designed to interfere with this system, the angiotensin-converting enzyme (ACE) inhibitors, have already yielded significant benefits in the treatment of hypertension and heart failure. Now, a new generation of agents, the angiotensin II receptor antagonists (more specifically AT-1 or type 1 receptor antagonists) are entering clinical practice and providing a more potent and specific way to target the RAS. Irbesartan, a highly specific AT-1 receptor antagonist which will be available in Canada in the near future, exhibits an excellent antihypertensive efficacy and tolerability profile with an incidence of reported adverse events comparable, and in some cases lower, than placebo.

Introduction

The rate of progress in decreasing cardiovascular mortality in North America has declined in recent years. As well, worldwide trends in cardiovascular disease are far from uniform. In some countries, mortality from cardiovascular disease has decreased substantially, while in others, the rate is increasing. Arterial hypertension plays a major role in cardiovascular mortality and morbidity and when it is not adequately controlled has, despite the progress made, a major impact on public health. Indeed, in the Global Burden of Disease Study,[1] an international effort to assess the worldwide risk factors of morbidity and mortality, hypertension accounted for 5.8% of global disability, coming in at number three after malnutrition (11.7%) and tobacco use (6.0%).

The Veteran Administration Studies first demonstrated how patterns of mortality and morbidity could be affected differently by antihypertensive therapy.[2] In fact, in observations that would be confirmed in many subsequent studies, the VA studies demonstrated that there was marked improvement in stroke-related end-points which was out of proportion with the small or insignificant benefit seen in coronary heart disease end-points, especially in younger individuals. Unfortunately, the decrease in the incidence of stroke in the United States seems to have leveled off and may even be increasing again. When looking for potential explanations for this observation, it is sobering to consider the current state of hypertension awareness and control in North America. Recent epidemiologic studies confirm that hypertension is a very common disease and one that has not been adequately controlled with our currently available therapeutic armamentarium.

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The Canadian Heart Health Surveys recently examined the awareness, treatment and control status of hypertension in this country.[3] These surveys were cross-sectional, population-based cardiovascular disease risk factor evaluations that were conducted in each of the ten provinces between 1986 and 1992. Hypertension — defined as a blood pressure ≥140/90 mm Hg in individuals aged 18 to 74 years of age — was found in 22% of the population (26% of men, 18% of women), representing 4.1 million Canadians. Only 16% of hypertensive participants were treated and controlled, while 23% were treated but not controlled, 19% were not treated, and 42% were unaware of their hypertension. These findings demonstrate that, even in a population with universal access and frequent interactions with the health system, inadequately controlled hypertension remains a problem of massive proportions. The findings are similar to those reported in the United States by the third National Health and Nutrition Examination Survey (NHANES).[4]

It is also important to examine the rate of continuation of the presently available agents as this may shed light on the reasons why so many millions of patients remain inadequately controlled and therefore vulnerable to the potentially devastating complications of hypertension. A review of Medicaid records in California evaluated the continuation rates with current antihypertensive agents.[5] Under the Medicaid system all patients have access to drug therapy making this analysis relevant to the Canadian context. Overall, only a dismal 14% of patients maintained continuous antihypertensive therapy for one year after initiation. There were also marked differences in continuation rates among the classes of agents, with angiotensin-converting enzyme (ACE) inhibitors having the highest rate at one year (33%), while diuretics had the lowest (5%).

Similar findings were established by studies performed in Saskatchewan, where, after a five-year follow-up, only 20% of patients were still on diuretics and the rest was either noncompliant or had been changed to other therapies. The picture was not any better for ß-blockers. In contrast, significantly higher percentages of patients remained on ACE inhibitors or calcium channel blockers, presumably because these agents are better tolerated.[6] The road towards controlling hypertension and its enormous health implications appears to pass through a concentrated effort in basic research to better understand the pathophysiology of this disorder; the road continues through the development and evaluation of new types of effective and better-tolerated agents in well-designed clinical trials.

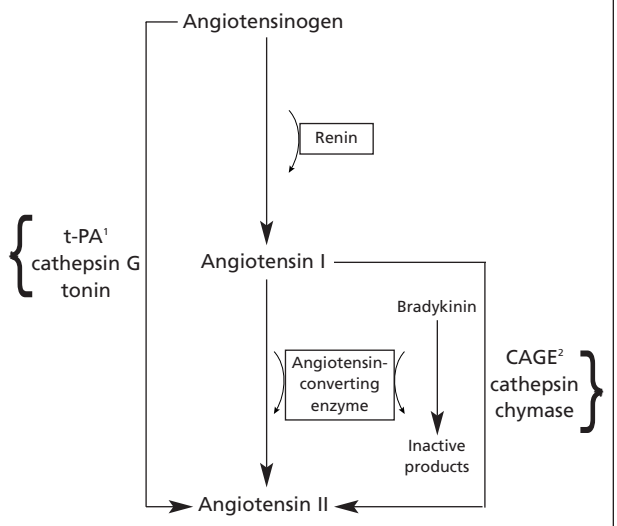
The renin-angiotensin system: A specific target for hypertension management

An issue of growing importance in clinical medicine is the role of the renin-angiotensin system (RAS) in the development of hypertension and vascular disease. The ability to target this system has become a very important addition to hypertension management, especially because evidence continues to grow of the role of angiotensin II, the end-product of the sequential activation of angiotensinogen by renin and ACE, in modifying vascular structure and function. The RAS exerts powerful influences on vasoconstriction and peripheral resistances, sympathetic function and cardiac performance. As well, it plays a role in regulating renal sodium and water handling, tubular-glomerular feedback, glomerular capillary pressure, antidiuretic hormone and aldosterone.

The classic view of the RAS is that of an acute endocrine system which increases peripheral resistances and blood pressure and maintains the volume of the extracellular fluid. As such, the system is an important part of the "flight or fight" response geared towards maintaining blood pressure homeostasis and defending the circulation against various perturbations.

Recently, however, a growing awareness has developed of the importance of chronic overactivity of the RAS, particularly at the target organ level. Consequences of this overactivity include myocardial hypertrophy, renal glomerular capillary hypertension and glomerulosclerosis, and in

Figure 1: Generation of angiotensin II



*Alternate pathways
[1]Tissue-type plasminogen activator.
[2]Chymostatin-sensitive angiotensin II-generating enzyme.

Table 1: Opposite effects of angiotensin receptors AT-1 and AT-2.

AT-1 Receptor	AT-2 receptor
– Vasoconstriction	– Vasodilatation
– Cell growth	– Cell growth inhibition
– Cell proliferation	– Cell differentiation
– Anti-natriuresis	– Natriuresis
– Production of: superoxide, aldosterone, endothelin, catecholamines, adhesion molecules, growth factors, plasminogen activator inhibitor-1 (PAI-1)	– Production of nitric oxide (NO, endothelium-derived relaxing factor)

blood vessels, alterations of structure and function resulting in decreased compliance. The tissue RAS functions at the local level in an autocrine or paracrine fashion more than in the classical endocrine function. As well as renin and ACE, a half-dozen independent pathways can activate the formation of angiotensin II (figure 1). Some of these pathways can convert angiotensinogen directly to angiotensin II, whereas others follow the more traditional pathway which includes angiotensin I as an intermediary. It is conceivable that the alternate pathways may indeed be just as important, or even more important, in the long term overactivity of the tissue RAS, raising the question: What is the best approach to block the system to prevent disease progression, as opposed to focusing exclusively on the antagonism of the classical endocrine pathway for short-term blood pressure control?

At the vascular level, the RAS has effects above and beyond vasoconstriction and a rise in blood pressure. A number of factors such as pressure, shear-stress, stretch, turbulence and vascular injury may induce a local increase in angiotensin II production. This leads to vascular remodelling and alterations in compliance and favors the development of atherosclerosis. Similar events take place in the heart where pressure overload, volume overload, cyclical stretch and an increase in wall tension leads to activation of the tissue RAS and the consequent functional and structural perturbations.

Similar arguments can be made regarding the influence of the tissue RAS in renal disease. Aging, hypertension and concomitant disease, such as diabetes, result in fewer filtering nephron segments. Each remaining nephron segment must assume more work and handle more blood flow. Adaptive mechanisms such as enlargement of the glomeruli and increased capillary pressure also lead to an increase in wall tension, shear-stress and turbulence within the glomeruli. These mechanisms are associated with the induction of local production of angiotensin II and other soluble mediators of fibrosis which impact the vascular endothelium and mesangial cells, causing conformational changes, some of which are irreversible. There exists, therefore, a very strong rationale to antagonize the RAS also from the standpoint of preventing the progression of renal disease.

ACE inhibitors are the first generation of agents to antagonize the RAS. They inhibit not only the production of angiotensin II, but also the breakdown of bradykinins which can result in both therapeutic and adverse effects. An entirely different therapeutic strategy is now being introduced with the advent of angiotensin II receptor antagonists. Two distinct angiotensin receptors have been identified: AT-1 which is linked to vasoconstriction, cell growth and hypertrophy; and AT-2 which mediates opposite effects such as the release of the vasodilator nitric oxide, growth inhibition and apoptosis (table 1). The new pharmacologic agents now being introduced into clinical practice antagonize the AT-1 receptor selectively.

Renin-angiotensin in hypertension: Pathophysiology and molecular genetics

Significant insight has been gained by basic research about the function of the angiotensin II receptors. Utilizing a transgenic mouse overexpressing the AT-1 receptor in a cardiac-specific fashion, Dzau and co-workers made seminal observations regarding the pathophysiology of the AT-1 receptor pathway in the heart.[7] Animals overexpressing the receptor in the myocardium had a significantly decreased survival and gene-dosage effect was observed. That is, there was an inverse correlation between survival and copy number of the transgene.

This was the first demonstration that cardiac overactivity of the AT-1 pathway causes lethality. Furthermore, treatment with captopril or the AT-1 antagonist losartan increased survival of the animals. Cardiac overexpression of the AT-1 receptor resulted in PR segment prolongation, widened QRS complexes and bradyarrhythmias, including heart block and other conduction system abnormalities. Autopsies of the transgenic animals revealed severe pulmonary edema, marked atrial dilatation, and ventricular hypertrophy and dilatation. These studies establish the significant pathological role of the activation of the AT-1 receptors in cardiac tissues and provide a strong rationale to block these receptors when the RAS is activated in disease conditions.

In contrast, molecular studies of the AT-2 receptor have shown that it modulates the growth response of the cell by putting a brake on many of the processes activated by the

Table 2: Angiotensin II receptor antagonists: Comparative human pharmacokinetics

Compound (active metabolite)	Bioavail-ability	Food effect	Active metabolite	Half-life (h)	%Protein Binding	Dosing (mg)	Volume of Distribution (L)
Irbesartan[a]	60%-80%	No	No	11-15	90.0	150-300 od	53-93
Losartan[b] (EXP 3174)*	33%	Minimal	Yes	2 6-9	98.7 99.8	50-100 od	34 12
Valsartan[c,d]	23%	Yes ↓46%	No	6	95.0	80-160 od	17

[a]Irbesartan U.S. product information
[b]Cozaar®(losartan) Canadian product monograph
*Active metabolite of losartan
[c]Diovan® (valsartan) Canadian product monograph
[d]Criscione L et al. *Cardiovasc Drug Rev* 1995;13:230-250

AT-1 receptor, such as myocyte hypertrophy, cell proliferation and collagen synthesis.[8] Animals in which the expression of the AT-2 receptors has been selectively deleted (gene knock-out) are hypertensive, exhibit an exaggerated pressor response to infused angiotensin II and respond to vascular injury with marked intimal hyperplasia suggesting that the loss of the counterbalancing effect of the AT-2 receptor has left unopposed the actions of the AT-1 receptor.[9] These findings lend additional support to the use of selective AT-1 antagonists since, unlike ACE inhibitors, they do not inhibit angiotensin II production and this ligand would then be available to bind the AT-2 receptor and mediate its potentially beneficial effects.

Angiotensin receptor blocker update

Irbesartan, a potent new selective antagonist of the AT-1 receptor

Irbesartan is a potent, specific and long-acting AT-1 receptor blocker. It is a non-peptidic, substituted biphenyl tetrazole. Irbesartan does not inhibit renin or ACE and does not result in bradykinin or prostaglandin accumulation which could be associated with a more favorable tolerability profile. As well, irbesartan has high affinity and specificity for the AT-1 receptor. Indeed, in various species and tissues, irbesartan was the most potent AT-1 receptor antagonist tested. It was 10-fold more potent than losartan as demonstrated in *in vitro* AT-1 receptor binding assays[10]

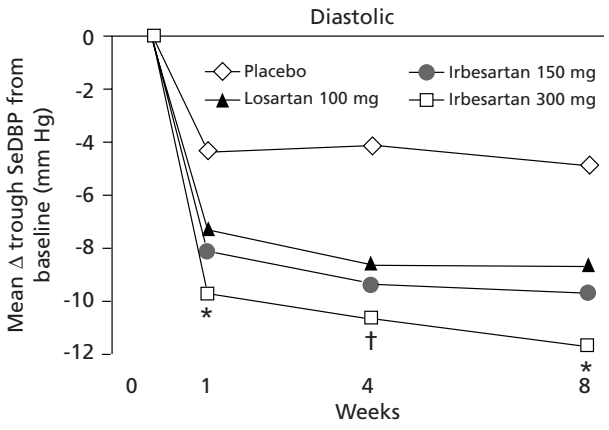
The activity of irbesartan at the AT-1 receptor was similar to that of saralasin, a non-specific angiotensin II receptor antagonist, but was 10,000-fold more specific for the AT-1 receptor than for the AT-2 receptor. Irbesartan displays dose-related and insurmountable antagonism of angiotensin II *in vitro* in rabbit aorta and *in vivo* in pithed rats. Its activity is evident independently of angiotensin II levels and, unlike losartan, does not require conversion to an active metabolite. Irbesartan is orally active and exhibits a high 60-80% bioavailability which is not affected by food, unlike valsartan. As well, it is highly protein bound (90%) and its plasma free fraction of approximately 10% limits the potential for interactions with highly plasma protein-bound drugs. In fact, no clinically significant drug interactions have been described with irbesartan. Other important properties of ibersartan include its:

- linear pharmacokinetics over the therapeutic dose-range
- rapid and complete absorption after oral administration
- long half-life of 11-15 hours
- volume of distribution which is the highest of all available AT-1 antagonists
- lack of accumulation with repeated dosing
- pharmacokinetic parameters which are similar regardless of age, gender and need for dose adjustment in elderly patients or those with hepatic or renal impairment (Table 2).

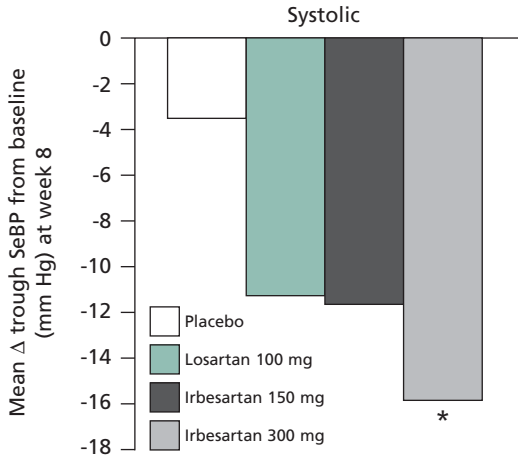
Comparing irbesartan with other antihypertensive agents

Several clinical trials this year have compared irbesartan with other drugs. One of the traditional agents, the β-blocker atenolol (50 mg titrated to 100 mg), was compared in a 30-site double-blind study with a low dose of irbesartan (75-150 mg). Both treatments significantly lowered blood pressure and there was no significant difference in efficacy between the groups. However, the safety and tolerability profile of irbesartan was better than that of atenolol. This resulted in a higher

Figure 2: Irbesartan vs losartan in mild-to-moderate hypertension



*P <0.01 irbesartan 300 mg vs losartan 100 mg at week 1 and 8.
†P <0.17 at week 4.
n=532



*P <.01 irbesartan 300 mg vs losartan 100 mg
P = NS irbesartan 150 mg vs losartan 100 mg
N shown at week 8
N = 532

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rate of therapy discontinuation in the atenolol group due to adverse effects.[11]

Two recent trials reported the results of comparative studies of irbesartan and the ACE inhibitor enalapril. A multinational, 51-site, double-blind study evaluated the full dose range of enalapril (maximum 40 mg daily) and irbesartan (maximum 300 mg daily) in patients with mild to moderate hypertension (seated diastolic blood pressure 95-110 mm Hg). Irbesartan was as effective as the full dose range of enalapril with a trend towards a lower incidence of adverse effects, especially cough.[12] A second randomized, multicenter, double-blind study compared the two agents in patients with severe hypertension (seated diastolic blood pressure of 115 to 130 mm Hg).[13] Patients were randomized to once-daily doses of irbesartan 150 mg or enalapril 20 mg, that were titrated to 300 mg and 40 mg, respectively. Open-label adjunctive therapy (hydrochlorothiazide, atenolol, and nifedipine) could be added after week 4 if blood pressure control was inadequate. The efficacy of both agents was equivalent with blood pressure normalization (trough seated diastolic blood pressure <90 mm Hg) being achieved in 59% of patients in the irbesartan group and in 57% in the enalapril-based group. Prior to week 12, although not statistically significant, reductions in trough blood pressure occurred earlier and fewer adjunctive medications and dose up titrations were necessary with irbesartan. Significantly, the incidence of side-effects was lower in the irbesartan group, with cough being the most prominent difference between the groups (13.1% with enalapril versus 2.5% with irbesartan, p=0.007).

A recent report compared the safety and efficacy of the calcium channel blocker amlodipine and irbesartan in hypertensive patients with type II diabetes mellitus and proteinuria.[14] In this randomized, double-blind study, both agents reduced trough seated diastolic pressure to a comparable degree, while the mean reductions in seated systolic blood pressure were slightly higher in the amlodipine group. However, marked differences were seen in renal effects as proteinuria decreased by 8.5% at 12 weeks in the irbesartan group while it increased by 19.7% in the amlodipine group. As well, there were significantly fewer adverse events with irbesartan than with amlodipine.

Of note, a clear relationship has been observed in these and other studies between irbesartan dose and reduction in blood pressure which was independent of patient age and gender. Remarkably, the greater efficacy at higher doses was not achieved at the expense of an increase in side-effects. In placebo-controlled clinical studies, the side-effect profile of irbesartan has been as good as, or better than, placebo. This represents a new paradigm of tolerability and efficacy in antihypertensive therapy since the dose-response relationship with this agent is highly favorable, while the side-effect profile does not change with dose escalation. This should be

contrasted with traditional antihypertensive agents such as diuretics and ß-blockers which exhibit a limited additional blood pressure-lowering dose-response and an escalating side-effect profile as doses are increased.

Are there clinically significant differences between the angiotensin II receptor (AT-1) antagonists?

This important issue has been addressed in recent studies. A large randomized trial, that included 1369 patients with mild to moderate hypertension, compared the effects of valsartan (titrated to 160 mg daily), losartan (up to 100 mg daily) or placebo.[15] Both AT-1 receptor antagonists, titrated up to the maximum recommended doses, reduced blood pressure significantly compared to placebo, but there were no differences in efficacy or response rates between the two agents.

A second study compared the antihypertensive efficacy and tolerabilty of irbesartan and losartan in patients with mild-to-moderate hypertension. This double-blind study included 567 patients randomized, after a placebo lead-in phase, in equal groups to placebo, losartan 100 mg, irbesartan 150 mg, or irbesartan 300 mg for 8 weeks.[16] The groups were well-matched for demographic and clinical characteristics. Both losartan and irbesartan were significantly better than placebo in lowering blood pressure, however, the main finding was that reductions in seated diastolic and systolic blood pressure with irbesartan 300 mg were significantly greater than with losartan 100 mg (by 3.1 and 5.1 mm Hg, respectively; $p<0.01$ for both comparisons) (figure 2). Normalization and response rates were also higher for irbesartan, but the differences were not statistically significant. A post-hoc analysis revealed that the incidence of adverse-events was significantly lower with irbesartan 300 mg than with losartan 100 mg ($p <0.05$) and presumably explain the lower discontinuation rates seen with the former.

Conclusion

The growing understanding of the pathophysiology of hypertension has revealed that the RAS has a prominent role in its development and complications. The poor tolerability of traditional antihypertensive agents is, at least in part, responsible for the dismal control of this worldwide epidemic. The introduction of AT-1 receptor antagonists — highly effective agents that have a safety and tolerability profile equivalent to placebo — provides an entirely new paradigm in antihypertensive therapy. Irbesartan is a highly specific and potent agent from this new category of drugs. Numerous clinical trials have shown its equivalency in terms of antihypertensive efficacy to other, much less well tolerated, traditional agents and recent studies demonstrate that irbesartan has greater potency compared to other available AT-1 antagonists. The mechanisms underlying irbesartan's superiority in these studies remain to be investigated but they could be related to its unique pharmacokinetic properties such as a higher bioavailabity, a longer half-life and a larger volume of distribution.

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