Angiotensin II-receptor antagonists: An overview

RAQUEL DINA AND MAHTAB JAFARI

Abstract: Angiotensin II (AT-II)-receptor antagonists are reviewed.

Research focused on blocking the renin–angiotensin system (RAS) led to the discovery of angiotensin-converting-enzyme (ACE) inhibitors, which are effective in the treatment of hypertension but are associated with a high frequency of cough and other adverse effects. AT-II-receptor antagonists were developed as agents that would more completely block the RAS and thus decrease the adverse effects seen with ACE inhibitors. AT-II-receptor antagonists include losartan, valsartan, irbesartan, candesartan, eprosartan, telmisartan, and tasosartan. Several clinical trials have demonstrated that AT-II-receptor antagonists are as effective as calcium-channel blockers, β-blockers, and ACE inhibitors in the treatment of hypertension and induce fewer adverse effects. The adverse effects of AT-II-receptor antagonists—dizziness, headache, upper-respiratory-tract infection, cough, and gastrointestinal disturbances—occur at about the same rate as with placebo. All available AT-II-receptor antagonists seem to be equally effective in reducing both systolic and diastolic blood pressure, and they are comparable in cost. Currently, AT-II-receptor antagonists are used either as monotherapy in patients who cannot tolerate ACE inhibitors or in combination with other antihypertensive agents.

Angiotensin II-receptor antagonists are well tolerated and are as effective as ACE inhibitors in decreasing blood pressure.

Index terms: Angiotensin-converting-enzyme inhibitors; Candesartan cilexetil; Eprosartan mesylate; Hypertension; Irbesartan; Losartan potassium; Mechanism of action; Telmisartan; Toxicity; Valsartan

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High blood pressure affects over 50 million Americans, but 14.8% of this population is untreated and 26.2% is inadequately treated; in another 31.6%, the condition remains undiagnosed. Hypertension is adequately controlled in only one patient out of four.[1] Lifestyle modifications and drug therapy can prevent most of the morbidity and mortality associated with this disease. When used properly, drug therapy can control the progression of end-organ damage.[2] The sixth report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-VI) recommended diuretics and β-blockers for the initial treatment of hypertension.[3] These agents are considered first line because of their proven ability to reduce cardiovascular-associated morbidity and mortality. JNC-VI also acknowledged that angiotensin-converting-enzyme (ACE) inhibitors, calcium-channel blockers, α_1-receptor blockers, α/β-blockers, and angiotensin-receptor antagonists are as efficacious as β-blockers and diuretics in reducing blood pressure.

This article provides an overview of the angiotensin II (AT-II)-receptor antagonists.

The renin–angiotensin receptor system

The renin–angiotensin–aldosterone cascade is activated when renin, secreted by the juxtaglomerular cells of the kidneys, catalyzes the conversion of angiotensinogen to angiotensin I (AT-I) in the liver. AT-I is locally transformed into active AT-II via ACE. AT-II, a peptide hormone, is responsible for numerous effects: aldosterone production and release, afferent and efferent vasoconstriction, proximal tubular reabsorption of sodium, increased inotropism and chronotropism, stimulation of drinking behavior and sodium appetite, vagus suppression, and β-adrenergic-receptor stimulation. Two subtypes of AT-II receptors have been identified. Type 1

RAQUEL DINA is a Pharm.D. degree candidate and MAHTAB JAFARI, PHARM.D., is Assistant Professor of Pharmacy Practice, Western University of Health Sciences, Pomona, CA.

Address reprint requests to Ms. Dina at 680 Mira Monte Place, Pasadena, CA 91101, or to raqueldina@aol.com.

receptors are predominantly found on vascular endothelium and are linked to all the known physiological and pharmacologic actions of AT-II. Stimulation of type 1 receptors by AT-II induces vasoconstriction, renal tubular sodium reabsorption, aldosterone release, vascular smooth muscle remodeling, and stimulation of central and peripheral sympathetic activity, thus leading to increases in blood volume and blood pressure.[4] Antagonism of type 1 receptors lowers blood pressure by inhibiting these actions. Type 2 receptors are predominantly found in the adrenal medulla, uterus, and fetal tissue and may play a role in fetal growth and differentiation, although the exact function of these receptors has not been identified.[2]

Inhibitors of the renin–angiotensin system

Research that focused on blocking the renin–angiotensin system (RAS) led to the discovery of ACE inhibitors, which proved efficacious in the treatment of hypertension, various cardiovascular disorders (e.g., congestive heart failure and coronary insufficiency), and renal diseases.[5] However, the high frequency of cough with ACE inhibitors (up to 20% of patients)[6,7] meant that another class of equally efficacious agents with a potentially more favorable adverse-effect profile was needed.

In addition to inhibiting the conversion of AT-I to AT-II, ACE inhibitors block the degradation of bradykinin via kininase II, which has enzymatic properties similar to those of ACE. Inhibition of bradykinin degradation is thought to be responsible for the cough commonly associated with ACE inhibitors.[8]

Conversion of AT-I to AT-II is not the only pathway for AT-II generation. AT-II is also formed via pathways involving cathepsin G, elastase, tissue plasminogen activator, chymostatin-sensitive AT-II-generating enzyme, and chymase; thus, ACE inhibition only partially reduces the formation of AT-II.[9] Agents that can specifically and selectively inhibit the action of AT-II could completely block the RAS. In addition, relative to other classes of antihypertensives, such agents might decrease the frequency of common adverse effects, such as dizziness, headache, fatigue, diarrhea, cough, and edema.[10]

Currently, two classes of drugs have the mechanistic potential to completely block the RAS: renin inhibitors and AT-II-receptor antagonists. Competitive antagonism of renin would prevent the formation of AT-II by inhibiting AT-I formation; however, the development of such agents has progressed slowly because of continuing problems with bioavailability.[11] Saralasin, the first AT-II-receptor antagonist, was synthesized in 1971. An intravenous formulation of this AT-II peptide analogue was shown to lower blood pressure in direct proportion to the plasma level of renin. However, saralasin was not a feasible treatment for hypertension because it had poor bioavailability and a short duration of action and because it potentiated vasoconstriction and induced hypertensive effects in low-renin conditions.[12]

Losartan potassium

Losartan potassium (Cozaar, Merck) was the first orally bioavailable, long-acting, nonpeptide AT-II type 1-receptor antagonist to be used in humans.[10,13] It has been extensively studied in both animals and human volunteers.[13] Its effectiveness as an antihypertensive agent has been established.[13,14]

Peak plasma concentrations of losartan are achieved within one hour of oral administration. Losartan has a half-life of 1.5–2.5 hours (Table 1).[15,16] It is rapidly absorbed from the gastrointestinal tract, independent of food intake. Losartan undergoes first-pass hepatic metabolism via cytochrome P-450 (CYP) isoenzymes 2C9 and 3A4 to its active carboxylic acid metabolite, EXP-3174, which reaches peak plasma concentration in two to four hours and has a half-life of six to nine hours.[15,16] Despite the biotransformation of losartan by CYP isoenzymes, no pharmacokinetic or pharmacodynamic interactions with warfarin or digoxin have been reported. The consequences of using losartan with potent CYP2C9 inhibitors have not been examined. In vitro studies have shown that oxidation of losartan to EXP-3174 is markedly inhibited by ketoconazole, a potent inhibitor of CYP3A4; however, the clinical consequences, if any, of this interaction have yet to be determined.[17]

Table 1.
Comparison of Angiotensin II-Receptor Antagonists

Drug	Active Metabolite	Bioavailability (%)	Daily Dose (mg)	Half-life (hr)	Cost ($)[a]
Losartan	Yes	33	25–100	2 (losartan) 6–9 (EXP-3174)	38
Valsartan	No	25	80–320	6	36
Irbesartan	No	60–80	150–300	11–15	36
Candesartan	No	42	8–32	3–4 3–11	36
Eprosartan	No	13	600–800	5–9	37
Telmisartan	No	42–58	20–80	24	39

[a]Estimated cost, based on average wholesale price (*Drug Topics Red Book*, 1999), to the pharmacist for a one-month supply at the usual starting dosage.

Several clinical trials have demonstrated the relative tolerability of losartan.[8,14,18-20] The most frequent adverse reaction, as observed in a clinical trial of 2900 patients assessing the safety and tolerability of losartan,[20] was dizziness, reported by 4.1% of patients taking losartan versus 1.3% of placebo recipients. Other adverse events (headache, upper-respiratory-tract infections, diarrhea, fatigue, and cough) occurred with similar frequencies in the losartan and placebo groups and thus were not considered drug related.

Unlike other AT-II-receptor blockers, losartan has a uricosuric effect after single or multiple doses in salt-depleted or salt-loaded normotensive patients,[21] sodium-repleted patients with essential hypertension,[22] and hypertensive patients with intrinsic renal disease.[23] The hypouricemic and uricosuric properties have been linked to the parent compound but not to its metabolite.[24] It is postulated that a decrease in serum uric acid levels could potentially be advantageous, but uricosuria may enhance the development of uric acid nephropathy.[21] However, uric acid nephropathy has not been reported thus far.

Once-daily administration of losartan is possible because the drug's effects are extended by the EXP-3174 metabolite, which is 40 times more potent than losartan[13] and has been found to produce consistent reductions in blood pressure over a 24-hour period.[18] The usual starting dosage of losartan potassium is 50 mg once daily. The dosage can be increased to a maximum of 100 mg daily. Doses exceeding 100 mg have not been found to produce any additional decrease in systolic or diastolic blood pressure.[18] In patients who have hepatic impairment or who may be volume depleted, such as those taking large doses of a diuretic, the starting dosage should be reduced to 25 mg once daily to minimize the occurrence of symptomatic hypotension.

Losartan potassium is marketed as a single-ingredient product and in combination with hydrochlorothiazide (Hyzaar, Merck; losartan potassium 50 mg plus hydrochlorothiazide 12.2 mg and losartan potassium 100 mg plus hydrochlorothiazide 25 mg). Use of the combination product may be appropriate if losartan monotherapy has failed to control blood pressure. The maximum antihypertensive effect is usually apparent within three weeks. The combination product is not recommended for patients with hepatic impairment because losartan is usually initiated in this group of patients at a dosage of 25 mg once daily. The combination product should also be avoided in patients with renal impairment (creatinine clearance [CL_{cr}], <30 mL/min).

Valsartan

Valsartan (Diovan, Novartis) was the second nonpeptide AT-II type 1-receptor antagonist available for the treatment of hypertension. Valsartan is rapidly absorbed from the gastrointestinal tract after oral administration and can be administered without regard to food intake.[25] The peak effect of valsartan is evident in two to four hours; the bioavailability is 25%. Valsartan has a half-life of six to nine hours and demonstrates antihypertensive effects for approximately 24 hours. Less than 10% of an orally administered dose of valsartan undergoes biotransformation in the liver; the enzymes responsible for its metabolism are unknown, and no active metabolites have been identified.[26] Elimination occurs primarily in the bile (86%) and to a lesser extent via the kidneys (13%), largely as unchanged drug.[27,28]

Dosages ranging from 80 to 320 mg once daily are effective for controlling blood pressure and are recommended in patients who are not volume depleted. Greater reductions in blood pressure are apparent with incremental increases in the dosage up to 320 mg/day; hence, it is recommended that valsartan be started at 80 mg/day and the dosage adjusted upward until the desired response is reached.[6] No reduction in the starting dosage is required in patients with mild to moderate hepatic or renal insufficiency or in the elderly. The effectiveness of valsartan 80–320 mg/day in reducing blood pressure was established by a randomized, double-blind, placebo-controlled trial.[6] In a comparative double-blind trial, valsartan 80 mg/day was as effective as enalapril maleate 20 mg/day and amlodipine 5 mg/day (as the besylate) in lowering the blood pressure of patients with mild to moderate hypertension.[29,30] In addition, valsartan 80 and 160 mg/day was as effective as enalapril 20 mg/day and lisinopril 10 or 20 mg/day in lowering blood pressure in patients with mild to moderate essential hypertension.[31,81] As is the case with other AT-II-receptor antagonists, hydrochlorothiazide acts additively to lower blood pressure in patients who do not achieve adequate blood pressure reduction with valsartan alone.[32,33]

The safety of valsartan has been assessed in various clinical trials.[34,35] Valsartan was well tolerated at dosages of 80–160 mg/day. At higher dosages (320 mg/day), dizziness became more prevalent (9.3% of patients, versus 3.4% for 80–160 mg/day). Headache, upper-respiratory-tract infection, diarrhea, and fatigue occurred most commonly (>1%), but at rates comparable to those in placebo recipients.[34] In one study, dry cough was considerably less common with valsartan (21.4%) than with the ACE inhibitors lisinopril (71.1%).[36] In another study comparing valsartan with an ACE inhibitor (enalapril) and with placebo, <2% of study patients reported cough.[29]

No clinically important pharmacokinetic interactions were reported when valsartan was given with digoxin, warfarin, glyburide, cimetidine, or hydrochlorothiazide. The most important laboratory finding was an increase in serum potassium of >20%

in 4.4% of patients taking valsartan versus 2.9% of patients taking placebo; however, no valsartan-treated patients who developed hyperkalemia discontinued the drug.[a]

Irbesartan

Irbesartan (Avapro, Bristol-Myers Squibb) is a long-acting nonpeptide AT-II type 1-receptor antagonist with a plasma half-life of 11–15 hours. Irbesartan has no active metabolites and is 90% protein bound. The drug is absorbed rapidly after oral administration and has a bioavailability of 60–80%, the highest in its class.[37] Food intake has no effect on absorption. After oral administration, peak plasma concentrations are achieved in two hours. Irbesartan undergoes hepatic metabolism via glucuronide conjugation and oxidation; no active metabolites have been identified. After administration of a single 150-mg dose of irbesartan, 20% of the dose is excreted renally and about 30% is excreted in the bile.[b] In vitro studies indicate that oxidation of irbesartan occurs primarily via CYP2C9. Warfarin and digoxin appear to have a negligible effect on CYP2C9 metabolism of irbesartan. When potential drug interactions were explored in patients taking warfarin, hydrochlorothiazide, or digoxin concurrently with irbesartan, no changes in the pharmacokinetics of digoxin or the pharmacodynamic effects of warfarin (prothrombin time) were noted.[38]

Antihypertensive effects are seen within two weeks of initiating therapy, with maximum effects occurring at between two and six weeks.[39-41] Effects on blood pressure are dose dependent over the range of 75–300 mg.[42,43] However, data from various double-blind, placebo-controlled trials show that daily doses of 150–300 mg, administered once daily or in divided doses, will effectively reduce blood pressure by 3.1–6.1 mm Hg.[42] The addition of hydrochlorothiazide 6.25–25 mg/day to irbesartan 75–300 mg/day further decreases blood pressure[40,44,45] to the same extent as treatment with enalapril 20–40 mg.[46]

In clinical studies of irbesartan there was no relationship between the dosage and the overall frequency of adverse reactions. The rates of serious adverse events were similar for irbesartan (1.0%) and placebo (1.9%).[47] The most common adverse reactions were headache (12% rate for irbesartan, 17% for placebo) and upper-respiratory-tract infection (9.0% for irbesartan, 5.1% for placebo).

The recommended starting dosage of irbesartan is 150 mg once daily; the dosage may be increased to 300 mg once daily with or without food for patients who require further blood pressure reduction. The starting dosage does not need to be reduced in the elderly or in patients with hepatic impairment or mild to severe renal impairment. Hydrochlorothiazide has an additive blood pressure-lowering effect, and the combination of irbesartan and hydrochlorothiazide may be useful when blood pressure is not controlled by irbesartan alone.[40,44,45] Irbesartan may also be administered with other antihypertensive agents. When irbesartan therapy is discontinued, the dosage does not need to be tapered, regardless of the daily dose administered, because abrupt withdrawal of the drug is not associated with an increase in blood pressure.[40] Likewise, loss of blood pressure regulation should not occur if a dose is missed.

Irbesartan is available as a single-ingredient product and in combination with hydrochlorothiazide (Avalide, Bristol-Myers Squibb; irbesartan 150 mg plus hydrochlorothiazide 12.5 mg and irbesartan 300 mg plus hydrochlorothiazide 12.5 mg). Use of this combination product should be reserved for patients who have not achieved the desired blood pressure-lowering effect with irbesartan monotherapy. It is recommended that this product be started at one tablet once daily. The maximum effect on blood pressure should be attained two to four weeks after therapy begins. No dosage adjustment is necessary in patients with hepatic impairment; however, the combination product is not recommended in patients with renal impairment (CL_{cr}, <30 mL/min).

Candesartan cilexetil

Candesartan cilexetil (Atacand, Astra Merck), another long-acting nonpeptide antagonist of AT-II type 1 receptors, is a prodrug that is hydrolyzed to its active metabolite candesartan during gastrointestinal absorption.[48] The half-life of candesartan is about nine hours, and it is 98% protein bound. About 60% of a dose is eliminated through the urine and 40% through the bile. Candesartan cilexetil and candesartan are not metabolized by CYP isoenzymes.

Candesartan cilexetil lowers blood pressure in a dose-dependent manner (at doses of up to 32 mg).[49-51] The 16- and 32-mg daily doses seem to be more effective than lower doses (4 and 8 mg/day) in lowering blood pressure; mean reductions in blood pressure were 10.7 and 12.6 mm Hg for candesartan cilexetil 16 and 32 mg, respectively, and 9.9 and 10.5 mm Hg for 4- and 8-mg doses.[49] After administration of 4–32 mg, peak plasma candesartan levels are achieved within three to four hours. Dosages of 4–16 mg/day have no effect on plasma aldosterone concentrations; however, a decrease in the plasma aldosterone concentration is seen when 32 mg/day is administered.

There have been no reports of clinically important interactions between candesartan and other agents commonly used by patients with hypertension (hydrochlorothiazide, warfarin, digoxin, nifedipine, glyburide, or the major components of oral contraceptives, levonorgestrel and ethinyl estradiol).[52] Interactions with drugs that inhibit or are metabolized by CYP isoenzymes would not be expected.

A randomized, double-blind, placebo-controlled, parallel-group study in patients with mild hypertension and type 2 diabetes mellitus showed that, after 12 weeks of therapy with candesartan cilexetil 8–16 mg once daily, systolic and diastolic blood pressure decreased by a mean of 7.1 and 6.3 mm Hg, respectively, and that greater than 69% of the patients had their blood pressure controlled.[53] Candesartan cilexetil had no effect on the lipid profiles or glucose homeostasis of diabetic patients. Mean hemoglobin A_{1c} levels were 7.1% at baseline and at 12 weeks in patients receiving candesartan cilexetil and 7.2% at baseline and 7.1% at 12 weeks in patients receiving placebo. Lipid profiles showed no significant changes between baseline and week 12, nor were there any differences between the candesartan and placebo groups.

Candesartan cilexetil is well tolerated, with no relationship seen between dosage or time of administration and occurrence of adverse events.[49,54-56] Headache (7%), upper-respiratory-tract infection (7%), pain (8%), and dizziness (4%) were among the most commonly reported adverse events, and these events generally resolved without discontinuation of therapy. Rates of adverse events were similar to those for placebo.[49,55]

The dosage of candesartan cilexetil must be individualized. When administered as monotherapy to patients who are not volume depleted, the usual staring dosage is 16 mg once daily with or without food. Dosages greater than 32 mg once daily have not been extensively studied and do not seem to be more effective than 32 mg/day for reducing blood pressure. An antihypertensive effect should be apparent in two weeks, with maximum reduction in blood pressure occurring within four to six weeks. If blood pressure is not controlled with candesartan cilexetil (8–16 mg/day) alone, a diuretic such as hydrochlorothiazide (12.5 mg/day) or another antihypertensive agent may be added.[57,58] No reduction in the starting dosage is necessary in patients who have mild renal or hepatic impairment or in the elderly.

Eprosartan mesylate

Eprosartan mesylate was the fourth selective nonpeptide AT-II type 1-receptor antagonist to gain approval for use in the treatment of hypertension in the United States. It was marketed by Unimed Pharmaceuticals in October 1999 under the name Teveten. After oral administration of a single dose of 300 mg of eprosartan, plasma concentration peaks in one to two hours in the fasted state.[59] Eprosartan is less bioavailable than other AT-II-receptor antagonists (Table 1); this may be related to incomplete absorption. Eprosartan yields no active metabolites after oral administration. It is eliminated primarily in bile (90%) and to a lesser extent in urine (7%) as unchanged drug. There is negligible systemic accumulation of eprosartan with long-term use, so dosage adjustment is not warranted in patients with hepatic or renal disease.

When eprosartan is used as monotherapy in patients who are not volume depleted, a starting dosage of 600 mg once daily is recommended. If a further decrease in blood pressure is warranted, the dosage may be increased to 800 mg/day.[59,60] In most patients it may take two to three weeks of treatment to see a maximum response in blood pressure. When used in combination with other antihypertensive agents, such as thiazide diuretics and calcium-channel blockers, an additive effect is seen[61,62]; however, a recommended starting dosage in this situation has not yet been established. Hypotension may occur in volume- or salt-depleted patients, so caution is needed in treating this patient population, and these conditions should be corrected before starting eprosartan therapy.

There appears to be a dose–response relationship between blood pressure decrease and dosage of eprosartan.[63] Neither the frequency of eprosartan administration nor an escalation in dosage is associated with an increase in adverse effects, as demonstrated by clinical studies that assessed dosages of up to 1200 mg/day.[64] Eprosartan has a relatively safe tolerability profile, with headache (10%), upper-respiratory-tract infection (8%), and myalgia (4%) being the most commonly reported adverse events (rates similar to those for placebo).[62,65] There is an extremely low rate of hyperkalemia associated with eprosartan (<0.2%).

Eprosartan does not inhibit CYP450 isoenzymes and is not metabolized via this pathway. Thus, eprosartan would not be expected to inhibit the metabolism of drugs that require this enzyme system for elimination (such as warfarin), nor should it be prone to drug interactions mediated by this pathway.[61,67] When administered with warfarin, eprosartan had no apparent influence on the anticoagulatory effect of warfarin, as determined by the International Normalized Ratio.[68] In conclusion, no dosage adjustments are necessary when eprosartan is administered with warfarin, digoxin, or glyburide.[61,67-69]

Telmisartan

Telmisartan (Micardis, Boehringer Ingelheim), a nonpeptide AT-II-receptor antagonist, gained FDA approval for use in the treatment of hypertension in 1998. After oral administration, peak concentrations are reached in 0.5–1 hour. The absolute bioavailability of telmisartan is dose dependent.[70,71] A dose of 40 mg achieves 40% bioavailability, whereas 160 mg is 58% bioavailable. The bioavailability of oral telmisartan is reduced slightly, but not significantly, by food. The half-life is 24 hours, which allows for once-daily administration. About 97% of a telmisartan

dose is eliminated unchanged in the feces via biliary excretion. Renal excretion does not contribute to telmisartan's elimination.

Given that CYP isoenzymes are not involved in telmisartan's metabolism, no interactions with drugs that inhibit or are metabolized by CYP isoenzymes would be expected, with the possible exception of interference with the metabolism of drugs metabolized by CYP2C19. When telmisartan is administered with digoxin, peak and trough plasma concentrations of digoxin are increased 49% and 20%, respectively. When telmisartan is given with warfarin there is no evidence of any change in the International Normalized Ratio.[c]

The antihypertensive effects of telmisartan 20–160 mg were assessed in clinical trials in patients with mild to moderate hypertension. Reductions in systolic and diastolic blood pressure were on the order of 6–8 and 6 mm Hg, respectively, with 20 mg/day; 9–13 and 6–8 mm Hg with 40 mg/day; and 12–13 and 7–8 mm Hg with 80 mg/day.[70,72] A further decrease in blood pressure was not seen with a larger dosage (120–160 mg/day). It is recommended that telmisartan be initiated at 40 mg/day with or without food; the dosage may be increased to up to 80 mg/day if further blood pressure reduction is needed. In situations in which even further blood pressure reduction is needed (beyond that achieved with 80 mg/day), the addition of hydrochlorothiazide has been found to produce incremental reductions.[73] Antihypertensive activity begins within 3 hours and is maintained for 24 hours.[71,74] A maximum reduction in blood pressure is evident in approximately four weeks. No reduction in the starting dosage is necessary in patients with mild to moderate renal impairment or the elderly. Caution should be used when administering telmisartan to patients with biliary obstructive disorders or hepatic insufficiency, since this agent is eliminated primarily by biliary excretion.

The overall frequency of adverse events with telmisartan 20–160 mg/day was reported to be similar to that with placebo.[72] Rates of upper-respiratory-tract infection (7%), dizziness (5%), back pain (3%), sinusitis (3%), and diarrhea (3%) were similar to the rates for placebo (6%, 6%, 1%, 3%, and 2%, respectively).[75] The rate of cough with telmisartan (15.6%) was comparable to that with placebo (9.6%) and significantly less than with lisinopril (60%).[76,77]

Tasosartan

The new drug application for tasosartan was withdrawn in March 1998 because of unresolved questions about safety, specifically liver toxicity that occurred in 12% of patients in Phase II and Phase III clinical trials.

Comparative efficacy

Other antihypertensive classes. Several clinical trials have demonstrated that AT-II-receptor antagonists are as effective as other antihypertensive classes (calcium-channel blockers, β-blockers, and ACE inhibitors) in lowering blood pressure.[29,31,46,50,66,78-85]

Several AT-II-receptor antagonists have been compared with several ACE inhibitors (Table 2). A double-blind, multicenter, randomized study of 227 patients with mild to moderate hypertension evaluated the efficacy of candesartan cilexetil 4–8 mg once daily and enalapril maleate 10–20 mg once daily for eight weeks.[56] These two agents were equally efficacious. Mean reductions in sitting systolic and diastolic blood pressure were 10.5 and 10.1 mm Hg with candesartan and 15.0 and 12.3 mm Hg with enalapril. Adverse reactions were more frequent in the enalapril group (23.5%) than in the candesartan group (11.3%). Headache and cough were among the most common adverse events.

In another study, irbesartan and enalapril were compared for antihypertensive efficacy and tolerability in 182 patients with severe hypertension.[46] The primary endpoint was a reduction in diastolic blood pressure to normal (<90 mm Hg) or a reduction at week 12 of ≥10 mm Hg from baseline. At the end of the study period, 59% of the irbesartan recipients and 57% of the enalapril group had normal diastolic blood pressure. Response rates were similar in the irbesartan and the enalapril groups (100% and 98%, respectively). Irbesartan was associated with a lower rate of adverse events (55%) than enalapril (64%). A significantly higher percentage of patients receiving enalapril than irbesartan had cough (13.1% versus 2.5%). The results demonstrate that irbesartan is as effective as and more tolerable than enalapril, which might contribute to improved patient compliance.

A study comparing eprosartan and enalapril in patients with mild to moderate hypertension (n = 528) and patients with severe hypertension (n = 118) yielded results similar to those of comparisons between other AT-II-receptor antagonists and ACE inhibitors.[66,82] In the patients with mild to moderate hypertension, eprosartan and enalapril produced similar decreases in systolic and diastolic blood pressure—reductions of 15.5 and 12.9 mm Hg, respectively, with eprosartan 600 mg/day and reductions of 14.7 and 11.9 mm Hg with enalapril maleate 20 mg/day. Among the patients with severe hypertension, systolic blood pressure was reduced by 29.1 mm Hg and diastolic blood pressure by 20.1 mm Hg in those given eprosartan and by 21.1 and 16.2 mm Hg in those given enalapril. Eprosartan was at least as effective in reducing blood pressure as enalapril and was associated with a lower frequency of dry cough (2.2% versus 20.5%).

Candesartan, losartan, and irbesartan. Several trials have compared AT-II-receptor antagonists. One study involving 334 patients with

Table 2.
Clinical Trials Comparing Angiotensin-II-Receptor Antagonists with Angiotensin-Converting-Enzyme Inhibitors[a]

Reference	*n*	Baseline BP (mm Hg)	Dosage in mg/Day (Duration in wk)	Mean or Mean ± S.D. Reduction in SBP/DBP (mm Hg)	Response Rate (%)	Overall Efficacy
Losartan						
79	200	DBP, 95–120	Losartan 50 (12)	10.6 ± 13.0/8.4 ± 7.1	51	Losartan = enalapril
	199		Enalapril 20 (12)	12.9 ± 12.9/10.6 ± 7.2	59	
80	576 (total)	DBP, >95	Losartan 10 (8)	8.5 ± 14.5/7.3 ± 9.4	NR	Enalapril > losartan
			Losartan 25 (8)	11.6 ± 14.5/9.9 ± 8.5		
			Losartan 50 (8)	14.7 ± 11.8/11.9 ± 9.2		
			Losartan 100 (8)	12.3 ± 14.4/10.4 ± 8.9		
			Losartan 150 (8)	13.5 ± 11.9/13.1 ± 9.0		
			Enalapril 20 (8)	18.7 ± 15.4/16.2 ± 0.4		
Valsartan						
29	137	162/101	Valsartan 80 (8)	12.4 ± 13.7/9.5 ± 7.4	54	Valsartan = enalapril > placebo
	69	161/102	Enalapril 20 (8)	13.1± 13.3/9.4 ± 8.4	58	
	142	161/102	Placebo (8)	5.7 ± 14.2/4.5 ± 7.5	20	
31	364	DBP, 95–120	Valsartan 80–160 (12)	8.96 ± 14.95/5.25 ± 4.41	44.1	Valsartan = lisinopril > placebo
	187		Lisinopril 10–20 (12)	10.98 ± 14.94/6.93 ± 4.45	57.2	
	183		Placebo (12)	1.73 ± 14.39/3.23 ± 4.43	21.3	
81	184 (total)	165/102	Valsartan 80 ± HCTZ 12.5 (12)	38.5/13.2[b]	60.6	Valsartan = enalapril
		169/103	Enalapril 20 ± HCTZ 12.5 (12)	1.6/12.0	52.6	
Irbesartan						
46	121	DBP, 115–130	Irbesartan 150–300 (12)	40.1/29.6	59	Irbesartan = enalapril
	61		Enalapril 20–40 (12)	39.3/30.5	57	
83	98	164/101	Irbesartan 75–300 (12)	18.0 ± 13.5/13.0 ± 4.1	66	Irbesartan = enalapril
	102	165/102	Enalapril 10–40 (12)	18.0 ± 12.8/14.0 ± 4.2	63	
Candesartan						
56	80	DBP, 95–109	Candesartan 4–8 (8)	12.3 ± 12.0/10.1 ± 6.6	70	Candesartan = enalapril > placebo
	81		Enalapril 10–20 (8)	15.0 ± 12.2/10.5 ± 6.6	72	
	44		Placebo (8)	5.3 ± 11.0	43	
Eprosartan						
82	528 (total)	DBP, >114, SBP, >95	Eprosartan 400–600 ± HCTZ 12.5–25 (26)	15.5 ± 1.1/12.9 ± 0.6	81.7	Eprosartan > enalapril
			Enalapril 5–20 ± HCTZ 12.5–25 (26)	14.7 ± 1.0/11.9 ± 0.6	73.4	
66	59	DBP, 115–125	Eprosartan 400–600 ± HCTZ 25 (10)	29.1 ± 2.9/20.1 ± 2.1	69.5	Eprosartan = enalapril
	59		Enalapril 10–40 ± HCTZ 25 (10)	21.1 ± 2.7/16.2 ± 2.0	54.2	
Telmisartan						
71	139	DBP, 115–130	Telmisartan 20–80 ± HCTZ 12.5–25 (26)	22.1 ± 18.4/12.8 ± 5.2	63	Telmisartan = enalapril
	139		Enalapril 5–20 ± HCTZ 12.5–25 (26)	20.1 ± 15.6/11.4 ± 5.1	62	
84	385	DBP, >95	Telmisartan 40–160 ± HCTZ 12.5–25 (52)	23.8/16.6	83	Telmisartan = lisinopril
	193		Lisinopril 10–40 ± HCTZ 12.5–25 (52)	19.9/15.6	87	

[a]Losartan dosages are expressed in terms of losartan potassium, and candesartan dosages are expressed in terms of candesartan cilexetil. BP = blood pressure, SBP = systolic blood pressure, DBP = diastolic blood pressure, NR = not reported, HCTZ = hydrochlorothiazide.
[b]Primary efficacy variable was assessed after eight weeks of therapy.

mild to moderate hypertension showed that candesartan cilexetil 8 mg once daily is as effective as losartan potassium 50 mg once daily, but candesartan cilexetil 16 mg once daily had a greater blood pressure-lowering effect than losartan potassium 50 mg once daily.[50,54] At 24 hours after a dose, there was a 3.7-mm Hg

difference in sitting diastolic blood pressure and a 4.6-mm Hg difference in sitting systolic blood pressure between candesartan cilexetil 16 mg once daily and losartan potassium 50 mg once daily, in candesartan's favor.[54] In addition, the response rate was significantly higher in patients who received candesartan cilexetil 8 or 16 mg/day (50% and 57%, respectively) than in those given placebo (15%) or losartan (46%).

Another study compared the tolerability and antihypertensive efficacy of irbesartan and losartan in 567 patients with mild to moderate hypertension.[86] Irbesartan 150 or 300 mg and losartan potassium 100 mg were administered daily for eight weeks. Systolic blood pressure and diastolic blood pressure were reduced more by irbesartan 300 mg (16.4 and 11.7 mm Hg, respectively) than by losartan potassium 100 mg (11.3 and 8.7 mm Hg). At the end of the study, 52% of patients who received irbesartan 300 mg had normal blood pressure, compared with 42% of patients given losartan potassium 100 mg. Irbesartan 150 mg produced reductions in systolic and diastolic blood pressure (12.1 and 9.7 mm Hg, respectively) similar to those achieved by losartan potassium 100 mg (11.3 and 8.7 mm Hg). Both agents were well tolerated, as was found in previous trials.[18,20,40,43]

The results of these two studies suggest that candesartan and irbesartan are slightly more effective than losartan. Additional studies are needed to confirm these findings and to evaluate the effect of AT-II-receptor antagonists on hypertension-associated morbidity and mortality.

Combination therapy. Several studies have evaluated the efficacy of AT-II-receptor antagonists in combination with hydrochlorothiazide.[58,66,71,81,82,84,87] Blood pressure response was enhanced to various degrees when hydrochlorothiazide 12.5–25 mg was administered concurrently with an AT-II-receptor antagonist, relative to the response to monotherapy with an AT-II-receptor antagonist.

It has been postulated that therapy with an AT-II-receptor antagonist in combination with an ACE inhibitor will completely block the RAS.

Adverse reactions

Dizziness, headache, upper-respiratory-tract infection, cough, and gastrointestinal disturbances have been reported with AT-II-receptor antagonists at about the same rates as with placebo. All AT-II-receptor antagonists are less likely than ACE inhibitors to cause cough. Thus, it may be clinically advantageous to use an AT-II-receptor antagonist in patients who develop ACE inhibitor-induced dry cough.

Intravascular volume and renal function depend in part on the RAS. Patients who are volume depleted, are being treated aggressively with diuretics, are hyponatremic, or have progressive renal insufficiency or renal artery stenosis are at a greater risk of hypotension and deterioration of renal function. Therapy with AT-II-receptor antagonists in patients with these conditions should be initiated at a reduced dosage, or the underlying condition should first be corrected.

Like ACE inhibitors, AT-II-receptor antagonists may induce hyperkalemia in patients with chronic renal failure and in those receiving potassium-sparing diuretics or potassium supplements. Although hyperkalemia and renal insufficiency are more likely to occur in certain at-risk patients (e.g., patients with severe congestive heart failure), serum potassium and renal function must be monitored in all patients. However, in clinical trials of AT-II-receptor antagonists, clinically important changes in serum potassium levels were reported for valsartan only.

AT-II-receptor antagonists, like ACE inhibitors, are contraindicated in pregnant women and those who may become pregnant because direct action on the RAS can cause fetal morbidity and death.

Drug interactions

Of the AT-II-receptor antagonists, only candesartan has any clinically important interactions with digoxin, warfarin, and hydrochlorothiazide. Candesartan may increase serum concentrations of digoxin and may decrease warfarin concentrations; however, there is no apparent change in the International Normalized Ratio.

Losartan is metabolized by the CYP isoenzyme system; however, the effects of potent inhibitors of CYP3A4 and CYP2C9 on losartan pharmacokinetics have not been clinically studied. When administered with losartan, phenobarbital causes a 20% reduction in serum concentrations of losartan and its metabolite, thus reducing its effectiveness. Eprosartan, candesartan, irbesartan, valsartan, and telmisartan are not metabolized by the CYP system.

Cost

All the available AT-II-receptor antagonists, when prescribed at usual starting dosages, are similar in cost. Average wholesale prices, rounded to the nearest dollar, for a one-month supply of medication are as follows: candesartan cilexetil 16 mg/day, irbesartan 150 mg/day, and valsartan 80 mg/day, $36; losartan potassium 50 mg/day, $38; telmisartan 40 mg/day, $39; and eprosartan mesylate 600 mg/day, $37.[88]

Instructions for the patient

Women of childbearing age should be advised of the consequences of second- and third-trimester fetal exposure to AT-II-receptor antagonists and should be instructed to report their pregnancy to their physician as soon as possible. Patients taking losartan should be advised not to use potassium supplements or salt substitutes containing potassium because of the potential for increased serum potassium levels.

Indications

All currently available AT-II-receptor antagonists have received FDA-approved labeling for use in the treatment of hypertension either alone or in combination with other antihypertensive agents.

Several large trials are under way to evaluate the effects of AT-II-receptor antagonists on cardiovascular-associated morbidity and mortality in patients with hypertension and congestive heart failure. The LIFE (Losartan Intervention for Endpoint Reduction in Hypertension) study will, in hypertensive patients with documented left ventricular hypertrophy, evaluate long-term effects of losartan versus atenolol on cardiovascular morbidity and mortality. The Valsartan Heart Failure Trial (Val-HeFT), a multinational trial involving more than 4000 patients with congestive heart failure, will evaluate the addition of valsartan to current standard treatments for heart failure, including ACE inhibitors.

The ELITE (Evaluation of Losartan in the Elderly) study compared the efficacy and safety of losartan and captopril in 722 elderly patients (≥65 years old) with class II–IV heart failure and ejection fraction below 0.40.[89] Patients were treated with captopril 50 mg three times daily or losartan potassium 50 mg once daily for 48 weeks. There was no difference in the frequency of renal dysfunction (persistent increases in serum creatinine concentration) between the captopril and losartan groups (10.5% in each group). The rate of mortality from all causes was lower in the losartan group (4.8%) than in the captopril group (8.7%). Fewer losartan recipients than captopril recipients discontinued therapy because of adverse reactions (12.2% versus 20.8%). The results of this study have led to an additional study, ELITE II, to confirm the findings.

Formulary recommendations

Angiotensin-II-receptor antagonists seem to be as effective as ACE inhibitors for treating hypertension and can be initiated in patients who are unable to tolerate an ACE inhibitor. All available AT-II-receptor antagonists seem to be equally effective in reducing both systolic and diastolic blood pressure, and they are comparable in cost.

Losartan is unique among AT-II-receptor antagonists in that it has the ability to increase uric acid excretion, which in turn lowers plasma uric acid levels[22]; however, the clinical importance of this characteristic has yet to be determined.

Conclusion

Angiotensin-II-receptor antagonists are well tolerated and are as effective as ACE inhibitors in decreasing blood pressure. Currently, AT-II-receptor antagonists are used either as monotherapy in patients who cannot tolerate ACE inhibitors or in combination with hydrochlorothiazide or other antihypertensive agents.

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[a]Valsartan data on file. Novartis, East Hanover, NJ; 1996.

[b]Chando TJ, Everett DW, Kahle AD et al. Biotransformation of irbesartan in man. Data on file. Bristol-Myers Squibb, Princeton, NJ; 1997.

[c]Telmisartan data on file. Boehringer Ingelheim, Ridgefield, CT; 1998.

References

1. Burt VL, Whelton P, Roccella JR et al. Prevalence of hypertension in the US population. Results from the Third National Health and Nutrition Examination Survey, 1988-1991. *Hypertension*. 1995; 25:305-13.
2. Dzau VJ, Mukoyama M, Pratt RE. Molecular biology of angiotensin receptors: target for drug research? *J Hypertens.* 1994; 12:S1-5.
3. The 6th report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Bethesda, MD: National Heart, Lung, and Blood Institute National High Blood Pressure Education Program, 1997; NIH publication no. 98-4080.
4. Bernstein KE, Berk BC. The biology of angiotensin II receptors. *Am J Kidney Dis.* 1993; 22:745-54.
5. Timmermans PB, Chiu AT, Herblin WF et al. Angiotensin II receptor subtypes. *Am J Hypertens.* 1992; 5:406-10.
6. Neutel JM, Weber M, Pool J et al. Valsartan, a new angiotensin II antagonist: antihypertensive effects over 24-hours. *Clin Ther.* 1997; 19:447-57.
7. Simon TA, Gelarden T, Freitag SA et al. Safety of irbesartan in the treatment of mild to moderate systemic hypertension. *Am J Cardiol.* 1998; 82:179-82.
8. Lacourciere Y, Lefebvre J, Nakhle G et al. Association between cough and angiotensin converting enzyme inhibitors versus angiotensin II antagonists: the design of a prospective, controlled study. *J Hypertens.* 1994; 12(suppl):49S-53S.
9. Ellis ML, Patterson JH. A new class of antihypertensive therapy: angiotensin II receptor antagonists. *Pharmacother.* 1996; 16: 849-60.
10. Timmermans PB, Carini DJ, Chiu AT et al. Nonpeptide angiotensin II receptor antagonists. *Am J Hypertens.* 1009; 3:599-604.
11. Frishman WH, Fozailoff A, Bin C et al. Renin inhibition: a new approach to cardiovascular therapy. *J Clin Pharmacol.* 1994; 34: 837-80.
12. Case DB, Wallace JM, Keim HJ et al. Usefulness and limitations of saralasin, a weak competitive agonist of angiotensin II, for evaluating the renin and sodium factors in hypertensive patients. *Am J Med.* 1976; 60: 825-36.
13. Wong PC, Price WA Jr, Chiu AT et al. Nonpeptide angiotensin II receptor antagonists, XI: pharmacology of EXP3174: an active metabolite of DuP 753, an orally active antihypertensive agent. *J Pharmacol Exp Ther.* 1991; 259:861-70.
14. Nelson E, Merrill D. Efficacy and safety of oral MK-954 (DuP753), an angiotensin receptor antagonist, in essential hypertension. *J Hypertens.* 1991; 9:468S-9S.
15. Christen Y, Waeber B, Nussberger J et al. Oral administration of DuP 753, a specific angiotensin II receptor antagonist, to normal male volunteers: inhibition of pressor response to exogenous angiotensin I and II. *Circulation.* 1991; 83:1333-42.
16. Munafo A, Christian Y, Nussberger J et al. Drug concentration response relationships in normal volunteers after oral administration of losartan, an angiotensin II receptor antagonist. *Clin Pharmacol Ther.* 1992; 51: 513-21.
17. Yun CH, Lee HS, Rho JK et al. Oxidation of the angiotensin II receptor antagonist losartan (DUP753) in human liver microsomes. Role of cytochrome P4503A4 in formation of the active metabolite EXP3174. *Drug Metab Dispos.* 1995; 23:285-9.
18. Weber MA. Clinical experience with the angiotensin II receptor antagonist losartan. A preliminary report. *Am J Hypertens.* 1992; 5 (12, part 2):247S-51S.
19. Brunner HR, Christian Y, Munafo A et al. Clinical experience with angiotensin II receptor antagonists. *Am J Hypertens.* 1992; 5 (12, part 2):243S-6S.
20. Goldberg AI, Dunlay MC, Sweet CS. Safety and tolerability of losartan potassium, an angiotensin II receptor antagonist, compared with hydrochlorothiazide, atenolol, felodipine ER, and angiotensin converting enzyme inhibitors for the treatment of systemic hypertension. *Am J Cardiol.* 1995; 75: 793-5.

21. Burnier M, Rutschmann B, Nussberger J et al. Salt-dependent renal effects of an angiotensin II antagonist in healthy subjects. *Hypertension.* 1993; 22:339-47.
22. Tsunoda K, Abe K, Hagino T et al. Hypotensive effect of losartan, a nonpeptide angiotensin II receptor antagonist, in essential hypertension. *Am J Hypertens.* 1993; 6:28-32.
23. Gansevoort RT, de Zeeuw D, Shahinfar S et al. Effects of the angiotensin II antagonist losartan in hypertensive patients with renal disease. *J Hypertens.* 1994; 12:S37-42.
24. Sweet CS, Bradstreet DC, Berman RS et al. Pharmacodynamic activity of intravenous E-3174, an angiotensin II receptor antagonist, in patients with essential hypertension. *Am J Hypertens.* 1994; 7:1035-40.
25. Flesch G, Muller P, Lloyd P. Absolute bioavailability and pharmacokinetics of valsartan, an angiotensin II antagonist, in man. *J Hypertens.* 1997; 52:115-20.
26. Muller P, Flesch G, De Gasparo M et al. Pharmacokinetic and pharmacodynamic effects of the angiotensin II antagonist valsartan at steady state in healthy, normotensive subjects. *Eur J Clin Pharmacol.* 1997; 52:441-9.
27. Waldmeir F, Flesch G, Muller P et al. Pharmacokinetics, disposition and biotransformation of [^{14}C]-radiolabeled valsartan in healthy male volunteers after a single oral dose. *Xenobiotica.* 1997; 27(1):59-71.
28. Brookman LJ, Rolan PE, Palmer KR et al. Pharmacokinetics of valsartan in patients with liver disease. *Clin Pharmacol Ther.* 1997; 62:272-8.
29. Holwerda NJ, Fogari R, Angeli P et al. Valsartan, a new angiotensin II antagonist for the treatment of essential hypertension: efficacy and safety compared with placebo and enalapril. *J Hypertens.* 1996; 14:1147-51.
30. Corea L, Cardoni O, Fogari R et al. Valsartan, a new angiotensin II antagonist for the treatment of essential hypertension: A comparative study of the efficacy and safety against amlodipine. *Clin Pharmacol Ther.* 1996; 60:341-46.
31. Black HR, Graff A, Shute D et al. Valsartan, a new angiotensin II antagonist for the treatment of essential hypertension: Efficacy, tolerability and safety compared to an angiotensin converting enzyme-inhibitor, lisinopril. *J Hum Hypertens.* 1997; 483-9.
32. Benz JR, Black HR, Graff A et al. Valsartan and hydrochlorothiazide in patients with essential hypertension, a multiple dose, double-blind, monotherapy. *J Hum Hypertens.* 1998; 12:861-6.
33. Dallas Hall W, Montoro R, Little John T et al. Efficacy and tolerability of valsartan in combination with hydrochlorothiazide in essential hypertension. *Clin Drug Invest.* 1998; 16:203-10.
34. Oparil S, Dyke S, Harris F et al. The efficacy and safety of valsartan compared with placebo in the treatment of patients with essential hypertension. *Clin Ther.* 1996; 18:797-810.
35. Pool JL, Glazer R, Chiang YT et al. Dose-response efficacy of valsartan, a new angiotensin II receptor blocker. *J Hum Hypertens.* 1999; 13:275-81.
36. Benz J, Oshrain C, Henry D et al. Valsartan, a new angiotensin II receptor antagonist: a double blinded study comparing the incidence of cough with lisinopril and hydrochlorothiazide. *J Clin Pharmacol.* 1997; 37:101-7.
37. Brunner HR. The new angiotensin II receptor antagonist irbesartan: Pharmacokinetic and pharmacodynamic considerations. *Am J Hypertens.* 1997; 10(12, part 2):311S-7S.
38. Marino MR, Langenbacher KM, Ford NF et al. Pharmacodynamics and pharmacokinetics of irbesartan in patients with mild to moderate hypertension. *J Cardiovasc Pharmacol Ther.* 1999; 4(2):67-75.
39. Markham A. Irbesartan. A review of its pharmacodynamic and pharmacokinetic properties and therapeutic use in the management of hypertension. *Drugs.* 1997; 54:885-902.
40. Pool JL, Guthrie RM, Littlejohn TW III et al. Dose-related antihypertensive effects of irbesartan in patients with mild-moderate hypertension. *Am J Hypertens.* 1998; 11:462-70.
41. Van de Meiracker AH, Admiraal PJJ, Kroodsma JM et al. Hemodynamic and biochemical effects of the AT1 receptor antagonist irbesartan in hypertension. *Hypertension.* 1995; 25:22-9.
42. Reeves RA, Lin CS, Kassler-Taub K et al. Dose-related efficacy of irbesartan for hypertension: an integrated analysis. *Hypertension.* 1998; 31:1311-6.
43. Fogari R, Ambrosoli S, Corradi L et al. 24-hour blood pressure control by once daily administration of irbesartan assessed by ambulatory blood pressure monitoring. *J Hypertens.* 1997; 15:1511-8.
44. Marino MR, Langenbacher KM, Ford NF et al. Effect of hydrochlorothiazide on the pharmacokinetics and pharmacodynamics of the angiotensin II blocker irbesartan. *Clin Drug Invest.* 1997; 14:385-91.
45. Howe P, Phillips P, Saini R et al. The antihypertensive efficacy of the combination of irbesartan and hydrochlorothiazide assessed by 24-hour ambulatory blood pressure monitoring. Irbesartan Multicenter Study Group. *Clin Exp Hypertens.* 1999; 21:1373-96.
46. Larochelle P, Flack JM, Marbury TC et al. Effects and tolerability of irbesartan vs enalapril in patients with severe hypertension. *Am J Cardiol.* 1997; 80:1613-5.
47. Simon TA, Gelarden T, Freitag SA et al. Safety of irbesartan in the treatment of mild to moderate systemic hypertension. *Am J Cardiol.* 1998; 82:179-82.
48. Timmermans PB, Carini DJ, Chiu AT et al. Angiotensin II receptor antagonists. *Hypertension.* 1991; 18(suppl 3):136S-42S.
49. Rief M, White WB, Fagan TC et al. Effects of candesartan cilexetil in patients with systemic hypertension. *Am J Cardiol.* 1998; 82:961-5.
50. Sever P. Candesartan cilexetil: a new, long acting, effective angiotensin II type 1 receptor blocker. *J Hum Hypertens.* 1997; 11(suppl 2):S91-5.
51. Elmfeldt D, George M, Hubner R et al. Candesartan cilexetil, a new generation angiotensin II antagonist, provides dose dependent antihypertensive effects. *J Hum Hypertens.* 1997; 11(suppl 2):49S-53S.
52. Jonkman JHG, van Lier JJ, van Heiningen PNM et al. Pharmacokinetic drug interaction studies with candesartan cilexetil. *J Hum Hypertens.* 1997; 11(suppl 2):S31-5.
53. Trenkwalder P, Dahl K, Lehtovirta M et al. Antihypertensive treatment with candesartan cilexetil does not affect glucose homeostasis or serum lipid profile in patients with mild hypertension and type II diabetes. *Blood Press.* 1998; 7:170-5.
54. Andersson OK, Neldman S. The antihypertensive effect and tolerability of candesartan cilexetil, a new generation angiotensin II antagonist, in comparison with losartan. *Blood Press.* 1998; 7:53-9.
55. Bell TP, DeQuattro V, Lasseter KC et al. Effective dose range of candesartan cilexetil for systemic hypertension. *Am J Cardiol.* 1999; 83:272-5.
56. Zanchetti A, Omboni S, Di Biago C. Candesartan cilexetil and enalapril are of equivalent efficacy in patients with mild to moderate hypertension. *J Hum Hypertens.* 1997; 11 (suppl 2):S57-9.
57. Oparil S. Candesartan cilexetil in combination with low dose hydrochlorothiazide is effective in severe hypertension. *Am J Cardiol.* 1999; 84(10A):35S-41S.
58. Oparil S, Levine JH, Zuschke CA et al. Effects of candesartan cilexetil in patients with severe systemic hypertension. Candesartan Cilexetil Study Investigators. *Am J Cardiol.* 1999; 84:289-93.
59. Bottorff MB, Tenero DM. Pharmacokinetics of eprosartan in healthy subjects, patients with hypertension and special populations. *Pharmacotherapy.* 1999; 19(4, part 2):73S-8S.
60. Weber M. Clinical efficacy of eprosartan. *Pharmacotherapy.* 1999; 19(4, part 2):95S-101S.
61. Blum RA, Kazierad DJ, Tenero DM. A review of eprosartan pharmacokinetic and pharmacodynamic drug interaction studies. *Pharmacotherapy.* 1999; 19(4, part 2):79S-85S.
62. Gavras I, Gavras H. Safety and tolerability of eprosartan. *Pharmacotherapy.* 1999; 19(4, part 2):102S-7S.
63. Price DA, De'Oliveria JM, Fisher NDL et al. Renal hemodynamic response to an angiotensin II antagonist, eprosartan, in healthy men. *Hypertension.* 1997; 30(part 1):240-6.
64. Weber M. Efficacy and safety of eprosartan in patients with essential hypertension: Results of an 8-week, double blind, placebo controlled, multicenter trial. *J Hypertens.* 1998; 16(suppl 2):S2-45.
65. Hedner T, Himmelmann A, for the Eprosartan Multinational Study Group. The efficacy and tolerance of once and twice daily doses of eprosartan in essential hypertension. *J Hypertens.* 1997; 17:129-36.
66. Ponticelli C, for the Eprosartan Study Group. Comparison of the efficacy of eprosartan and enalapril in patients with severe hypertension. *Am J Hypertens.* 1997; 10:128A. Abstract.
67. Cox PJ, Bush BD, Gorycki PD et al. The metabolic fate of eprosartan in healthy subjects. *Exp Toxicol Pathol.* 1996; 48:340-1.

68. Kazierad DJ, Martin DE, Ilson B et al. Eprosartan does not affect the pharmacodynamics of warfarin. *J Clin Pharmacol.* 1998; 38:649-53.
69. Martin DE, Tompson D, Boike SC et al. Lack of effect of eprosartan on the single dose pharmacokinetics of orally administered digoxin in healthy male volunteers. *Br J Clin Pharmacol.* 1997; 43:661-4.
70. Meredith PA. Optimal dosing characteristics of the angiotensin I receptor antagonist telmisartan. *Am J Cardiol.* 1999; 84:7K-12K.
71. Karlberg BE, Lins LE, Hermansson K et al. Efficacy and safety of telmisartan, a selective AT1 receptor antagonist, compared with enalapril in elderly patients with primary hypertension. TEES Study Group. *J Hypertens.* 1999; 17:293-302.
72. Neutal JM, Smith DH. Dose response and antihypertensive efficacy of the AT_1 receptor antagonist telmisartan in patients with mild to moderate hypertension. *Adv Ther.* 1998; 15:206-17.
73. Neutal JM, Smith DH, Reilly PA. The efficacy and safety of telmisartan compared to enalapril in patients with severe hypertension. *Int J Clin Pract.* 1999; 53(3):175-8.
74. McClellan KJ, Markham A. Telmisartan. *Drugs.* 1998; 56:1039-46.
75. Meredith P. Optimal dosing characteristics of the angiotensin II receptor antagonist telmisartan. *Am J Cardiol.* 1999; 84:7K-12K.
76. Lacourciere Y. The incidence of cough: A comparison of lisinopril, placebo and telmisartan, a novel angiotensin II antagonist. Telmisartan Cough Study Group. *Int J Clin Pract.* 1999; 53(2):99-103.
77. Karlberg BE, Lins LE, Hermansson K. Efficacy and safety of telmisartan, a selective AT_1 receptor antagonist, compared with enalapril in elderly patients with primary hypertension. *J Hypertens.* 1999; 17:293-302.
78. Markham A, Goa KL. Valsartan. A review of its pharmacology and therapeutic use in essential hypertension. *Drugs.* 1997; 54:299-311.
79. Tikkanen I, Omvik P, Jensen H, for the Scandinavian Study Group. Comparison of the angiotensin converting enzyme inhibitor enalapril in patients with essential hypertension. *J Hypertension.* 1995; 13:1343-51.
80. Gradman AH, Arcuri KE, Goldberg AI et al. A randomized, placebo-controlled, double-blinded, parallel study of various doses of losartan potassium compared with enalapril maleate in patients with essential hypertension. *Hypertension.* 1995; 25:1345-50.
81. Mallion JM, Boutelant S, Chabaux P et al. Valsartan, a new angiotensin II antagonist; blood pressure reduction in essential hypertension compared with an angiotensin converting enzyme inhibitor, enalapril. *Blood Press Monit.* 1997; 2(4):179-84.
82. Gavras I, Gavras H. Effects of eprosartan versus enalapril in hypertensive patients on the renin-angiotensin-aldosterone system and safety parameters: Results from a 26-week, double-blind, multicenter study. Eprosartan Multinational Study Group. *Curr Med Res.* Opin. 1999; 15(1):15-24.
83. Mimran A, Ruilope RL, Kerwin L et al. A randomised double-blind comparison of the angiotensin II receptor antagonist, irbesartan, with the full dose range on enalapril for the treatment of mild-to-moderate hypertension. *J Hum Hypertens.* 1998; 12:203-8.
84. Neutal JM, Frishman WH, Oparil S et al. Comparison of telmisartan with lisinopril in patients with mild-moderate hypertension. *Am J Ther.* 1999; 6(3):161-6.
85. Tikkanen I, Omvik P, Jensen HA. Comparison of the angiotensin II antagonist losartan with the angiotensin converting enzyme inhibitor enalapril in patients with essential hypertension. *J Hypertens.* 1995; 13:1343-51.
86. Kassler-Taub K, Littlejohn T, Elliot W et al., for the Irbesartan Study Investigators. Comparative efficacy of two angiotensin II receptor antagonists, irbesartan and losartan, in mild to moderate hypertension. *Am J Hypertens.* 1998; 11:445-53.
87. Soffer BA, Wright JT, Pratt JH et al. Effects of losartan on a background of hydrochlorothiazide in patients with hypertension. *Hypertension.* 1995; 26:112-7.
88. Cardinale V, ed. Drug Topics red book. Montvale, NJ: Medical Economics; 1999.
89. Pitt B, Segal R, Martinez FA et al. Randomized trial of losartan versus captopril in patients over 65 with heart failure (Evaluation of Losartan in the Elderly Study, ELITE). *Lancet.* 1997; 349:747-52.