Angiotensin II receptor blockers

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The angiotensin II receptor blockers (ARBs) represent a newer class of antihypertensive agents. Their mechanism of action differs from that of the angiotensin-converting enzyme (ACE) inhibitors, which also affect the renin-angiotensin system. The ARBs were developed to overcome several of the deficiencies of ACE inhibitors: competitive inhibition of ACE results in a reactive increase in renin and angiotensin I levels, which may overcome the blockade effect; ACE is a relatively nonspecific enzyme that has substrates in addition to angiotensin I, including bradykinin and other tachykinins, and thus, inhibition of ACE may result in accumulation of these substrates; production of angiotensin II can occur through non-ACE pathways as well as through the primary ACE pathway, and these alternative pathways are unaffected by ACE inhibition; specific adverse effects are associated with ACE inhibitor effects on the enzyme; and ARBs may offer more complete angiotensin II inhibition by interacting selectively with the receptor site (1). All 7 drugs in this class are approved by the Food and Drug Administration for the treatment of hypertension, either alone or in combination with other drugs. Unlabeled uses include the treatment of congestive heart failure and, for losartan and irbesartan, diabetic nephropathy (2, 3).

Table 1. Pharmacokinetic parameters of angiotensin II receptor blockers*

Drug	Active metab	Bioavail (%)	Food effect	Half-life (hrs)		Protein binding (%)		Route of elimination (%)	
				Drug	Metab	Drug	Metab	Renal	Hepatic
Losartan	Yes	33	No	2	6–9	98.7	99.8	35	60
Valsartan	No	25	Yes	9	—	95	—	13	83
Irbesartan	No	70	No	11–15	—	90–95	—	20	80
Candesartan	Yes	42	No	3.5–4.0	3–11	99.5	—	33	67
Telmisartan	No	43	No	24	—	>99	—	0.5	>97
Eprosartan	No	15	No	5–7	—	98	—	7	90
Olmesartan	Yes	26	No	~13	—	>99	—	35–50	50–65

*Adapted from references 2 and 3.

Metab indicates metabolite; bioavail, bioavailability.

PHARMACOLOGY

The renin-angiotensin system, specifically angiotensin II, is implicated in the pathogenesis of essential hypertension, renovascular hypertension, congestive heart failure, and renal diseases associated with albuminuria (1, 4, 5). Blockade of the renin-angiotensin system with ACE inhibitors has provided effective treatment of these conditions; however, some of the adverse effects of ACE inhibitors appear to be unrelated to angiotensin II blockade. For example, cough and angioedema are due to other effects of ACE inhibition, such as degradation of bradykinins and prostaglandins (1).

The ARBs' mechanism of action, selective inhibition of angiotensin II by competitive antagonism of the angiotensin II receptors, has been speculated to reduce adverse effects and possibly improve clinical efficacy. ARBs displace angiotensin II from the angiotensin I receptor and produce their blood pressure–lowering effects by antagonizing angiotensin II–induced vasoconstriction, aldosterone release, catecholamine release, arginine vasopressin release, water intake, and hypertrophic response (4).

PHARMACOKINETICS/PHARMACODYNAMICS

The pharmacokinetic profiles of the agents in the ARB class are listed in *Table 1*. Losartan's major active metabolite, EXP-3174, is 10 to 20 times more potent than losartan and has a longer duration of action (1). The active metabolite is primarily responsible for the therapeutic effects. Candesartan and olmesartan are prodrugs that undergo metabolic activation during absorption from the gastrointestinal tract (1, 4, 5). The parent compounds of candesartan and olmesartan have little or no clinical efficacy. Once olmesartan is rapidly converted to its active metabolite, it does not undergo further metabolism (2).

CLINICAL COMPARISON OF ARBS

A review of the medical literature provided valuable information on the clinical trials that have been conducted on the agents in this class. *Table 2* summarizes the key findings of the clinical trials that were included in this review.

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Table 2. Comparative clinical trials involving angiotensin II receptor blockers

Study design (ref)	Drug, dosage, and number of patients	Results
8-week double-blind, randomized, multicenter (CLAIM II) (6)	Candesartan 16 mg x 2 weeks, then 32 mg x 6 weeks (307 patients) Losartan 50 mg x 2 weeks, then 100 mg x 6 weeks (304 patients)	At 8 weeks, candesartan lowered sitting BP more than losartan ($P < 0.05$). Response rates were 58.8% for candesartan and 52.1% for losartan*; difference has statistical significance but questionable clinical significance.
8-week double-blind, randomized, parallel, forced titration (7)	Candesartan 8 mg x 4 weeks, then 16 mg x 4 weeks (115 patients) Losartan 50 mg x 4 weeks, then 100 mg x 4 weeks (115 patients) Placebo (38 patients)	Both candesartan and losartan reduced systolic and diastolic BP when compared with placebo. Differences between candesartan 8 mg and losartan 50 mg were not significant. Candesartan 16 mg lowered systolic BP more effectively than either losartan dose ($P < 0.05$).
8-week double-blind, randomized, parallel (8)	Irbesartan 300 mg (142 patients) Irbesartan 150 mg (142 patients) Losartan 100 mg (141 patients) Placebo (142 patients)	Irbesartan 300 mg was superior to both irbesartan 150 mg and losartan 100 mg in lowering sitting diastolic BP ($P = 0.05$). Irbesartan 150 mg and losartan 100 mg did not differ in response. Irbesartan was better tolerated than losartan.
6-week double-blind, randomized (9)	Telmisartan 40 mg (57 patients) Telmisartan 80 mg (54 patients) Losartan 50 mg (57 patients)	Telmisartan 40 mg and 80 mg had significantly greater reductions of ambulatory BP assessment (from baseline) than losartan ($P < 0.05$).† Telmisartan 80 mg had greater reductions in diastolic and systolic BP from baseline than losartan at all evaluation periods.
4-way, double-blind, placebo-controlled crossover; patients received each drug for 4 weeks followed by a 2-week washout (10)	Losartan 50 mg (30 patients) Telmisartan 40 mg (30 patients) Valsartan 80 mg (30 patients)	Mean 24-hour diastolic BP was significantly lower with valsartan than with losartan or telmisartan ($P < 0.001$). Heart rate was not affected by any agent.
Randomized open-label crossover; patients received drug for 4 weeks followed by a 2-week washout (11)	Valsartan 80 mg (40 patients) Losartan 50 mg (40 patients)	Mean 24-hour BP, daytime and nighttime systolic and diastolic BP were lower with valsartan ($P < 0.01$). Trough/peak ratio of BP was significantly greater with valsartan ($P < 0.05$). (Both agents maintained antihypertensive effects throughout the 24 hours.)
8-week randomized, double-blind, placebo-controlled (12)	Valsartan 80 mg x 4 weeks, then 160 mg x 4 weeks (551 patients) Losartan 50 mg x 4 weeks, then 100 mg x 4 weeks (273 patients)	There was no significant difference between the 2 drug treatments. Valsartan showed a slightly greater response rate at the end of 8 weeks ($P < 0.021$).
8-week double-blind, randomized, parallel (13)	Olmesartan 20 mg (147 patients) Losartan 50 mg (150 patients) Valsartan 80 mg (145 patients) Irbesartan 150 mg (146 patients)	Reduction of sitting diastolic BP with olmesartan was greater than with losartan ($P = 0.0002$), valsartan ($P < 0.0001$), or irbesartan ($P = 0.0412$). Reductions of systolic BP were not significantly different. Reduction in mean 24-hour diastolic and systolic BP with olmesartan was significantly greater than with losartan and valsartan ($P \leq 0.05$).
Comparative trial‡	Eprosartan 600 mg (60 patients) Losartan 50 mg (60 patients)	Mean change in BP was greater for eprosartan but did not reach statistical significance.

*Response defined as a decrease in diastolic BP to <90 mm Hg or at least a decrease of 10 mm Hg.

†Ambulatory blood pressure assessed continuously throughout the 18- to 24-hour period after dosing.

‡Personal communication, Maryann T. Travaglini, PharmD, SmithKline Beecham Pharmaceuticals, April 2, 1998.

BP indicates blood pressure.

A metaanalysis of 43 randomized clinical trials (in 11,281 patients) comparing ARBs with placebo, drugs in other antihypertensive classes, and other ARBs found comparable blood pressure reductions for all ARBs; response rates were 48% to 55% (1, 4). The results of these trials suggest that candesartan, irbesartan, and telmisartan may be slightly more effective than losartan.

ADVERSE REACTIONS

In general, the ARBs are well tolerated. None of the drugs reviewed has a specific, dose-dependent adverse effect. Because cough is seen as a class effect of ACE inhibitors, studies with ARBs have specifically addressed this concern. The frequency of cough has been significantly lower in patients taking ARBs than in patients taking lisinopril (5). *Table 3* reviews the adverse reactions that have occurred in at least 2% of patients.

All of the ARBs are pregnancy category C for the first trimester and category D for the second and third trimesters.

DRUG INTERACTIONS

Comparison of the class as a whole reveals that losartan has the highest potential for drug interactions due to its involvement with the hepatic cytochrome P450 enzyme system (3). No sig-

Table 3. Adverse reactions from angiotensin II receptor blockers*

Adverse effects	Frequency (%)						
	Losartan n = 1075	Valsartan n = 2316	Irbesartan n = 1965	Candesartan n = 2350	Telmisartan n = 1455	Eprosartan n = 1202	Olmesartan n = 3278
Central nervous system							
Dizziness	3.5	—	—	4	—	—	3
Fatigue	—	2	4	—	—	2	—
Gastrointestinal							
Diarrhea	2.4	—	3	—	3	—	—
Dyspepsia	1.3	—	2	—	—	—	—
Abdominal pain	—	2	—	—	—	2	—
Musculoskeletal							
Arthralgia	—	—	—	—	—	2	—
Pain	—	—	—	3	1–3	—	—
Respiratory							
URTI	7.9	—	9	6	7	8	—
Cough	3.4	—	2.8	—	—	4	—
Sinusitis	—	—	—	—	3	—	—
Viral infection	—	3	—	—	—	2	—

*From references 2 and 3.

URTI indicates upper respiratory tract infection.

nificant drug interactions involving valsartan, irbesartan, or candesartan have been reported. Olmesartan is not metabolized by the cytochrome P450 enzyme system reducing the risk of interactions with drugs metabolized by these enzymes (2). *Table 4* summarizes significant drug interactions for this group of drugs.

SPECIAL PATIENT CONSIDERATIONS

The elderly and patients with renal or hepatic impairment

There are no specific considerations for the ARBs in the elderly or patients with renal or hepatic impairment. As with ACE inhibitors, acute renal failure may occur if these agents are given to patients with renal artery stenosis. In patients with mild to moderate hypertension who took part in the clinical trials, kidney function was not adversely affected; even in the presence of chronic renal insufficiency, ARBs are generally well tolerated, presumably because they are largely cleared in the bile (1).

Patients with heart failure

Several large, ongoing trials have been designed to evaluate the effects that ARBs have on morbidity and mortality in cardiac disease, including heart failure. The goal is to define the role of ARBs in therapy and compare it to that of ACE inhibitors. The results from the ELITE II trial suggest that treatment with losartan (50 mg daily) is not superior to treatment with captopril (50 mg 3 times daily) but is significantly better tolerated (14). Because the differences in morbidity or mortality rates associated with losartan and captopril are insignificant, losartan would be an appropriate choice for patients who are unable to tolerate ACE inhibitors (14).

The Val-HeFT study results suggest that adding valsartan to an ACE inhibitor does not improve survival (14). However, a subgroup analysis of patients not treated with an ACE inhibitor was performed which allowed comparison between valsartan (as monotherapy) and placebo. The results indicated reduced all-cause mortality and all-cause hospitalization (14, 15). This finding may well represent the strongest evidence to date that ARBs are comparable in efficacy to ACE inhibitors with regard to morbidity and mortality (14). The Candesartan in Heart Failure to Affect Reduction in Morbidity and Mortality (CHARM) study has 3 arms: comparison of candesartan to placebo as add-on therapy to an ACE inhibitor; of candesartan to placebo in patients unable to tolerate ACE inhibitors; and of candesartan to placebo in patients with symptomatic heart failure with preserved systolic function (ejection fraction >40%) (14). This study should be completed sometime in 2003 and will help better determine the role of ARBs as therapy in patients with heart failure.

DOSING AND ECONOMIC ISSUES

ARBs do not differ significantly in cost when prescribed once daily, as shown in *Table 5*. Losartan, candesartan, and eprosartan may require twice-daily dosing in some patients because of their short half-lives. Twice-daily dosing may substantially increase cost.

SUMMARY

The ARBs have very similar clinical profiles. They do, however, have different pharmacokinetic profiles, which may lead to some differences in efficacy. The newer agents irbesartan, candesartan, telmisartan, and olmesartan have longer half-lives and durations of action than the older agents losartan and valsartan (5). Twenty-four–hour blood pressure control could be more readily achievable with the newer agents. Losartan and valsartan may need to be administered twice daily in patients needing greater antihypertensive effects, whereas the agents with longer durations of action have no added benefit when administered

Table 4. Interactions of angiotensin II receptor blockers with other drugs*

Precipitant drug	Object drug	CYP450 substrates	Effect
Cimetidine	Losartan	—	↑ losartan no effect EXP3174
Fluconazole	Losartan	3A4, 2C9	↑ losartan
Indomethacin	Losartan	—	↓ hypotensive effect
Phenobarbital	Losartan	—	↓ losartan ↓ active metabolite
Rifampin	Losartan	3A4, 2C9	↓ losartan
Telmisartan	Digoxin	—	↑ digoxin

*Adapted from references 3 and 5.

Table 5. Dosing guidelines* and acquisition costs for angiotensin II receptor blockers

Drug	Starting dose (mg daily)	Maintenance dose (mg daily)	Acquisition cost for 1 month of therapy
Losartan	50	25–100 QD-BID†	$34.80 (50 mg) QD $69.60 (25 mg or 50 mg) BID
Valsartan	80	80–320 QD	$33.60 (80 mg) QD $36.90 (160 mg) QD
Irbesartan	150	150–300 QD	$37.20 (150 mg) QD $36.60 (300 mg) QD
Candesartan	16	8–32 QD-BID	$30.30 (16 mg) QD $60.60 (16 mg) BID
Telmisartan	40	20–80 QD	$34.50 (40 mg) QD $36.30 (80 mg) QD
Eprosartan	600	400–800 QD-BID	$32.10 (600 mg) QD
Olmesartan	20	20–40 QD	$30.90 (20 mg) QD $30.90 (40 mg) QD

*Adapted from references 3 and 4.

†Some patients will require the total daily dose to be split into twice-daily dosing.

QD indicates once a day; BID, twice a day.

more than once daily. Of course, a once-daily product is always preferred.

Several double-blind, head-to-head comparative trials have evaluated the relative antihypertensive efficacy of the ARBs in patients with mild to moderate hypertension. The net result is that the longer-acting agents may be more effective than losartan and valsartan at providing 24-hour blood pressure control. But, as also mentioned, a metaanalysis of 43 trials comparing the antihypertensive effects of ARBs found comparable antihypertensive efficacies within the ARB class (4, 5). Whether reported differences in efficacy are clinically relevant regarding morbidity and mortality has not been determined.

When evaluating differences among the ARBs, their current and future places in therapy for unlabeled uses must be considered. ARBs have been evaluated for use in heart failure, as combination therapy with ACE inhibitors and alone as standard therapy. Losartan and valsartan are the only ARBs for which studies have been completed that involved long-term follow-up with morbidity and mortality as endpoints. Neither agent can replace ACE inhibitors as first-line therapy, but both remain a rational alternative for patients unable to tolerate ACE inhibitors. Candesartan is currently being evaluated for this same use.

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