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## Perspective on Hypertension Treatment: Angiotensin II Blockers

In this issue, Dana Fox and Julie Martin present a review of a growing class of antihypertensive agents, the angiotensin II blockers. These products have an advantage over their cousins, the angiotensin converting enzyme (ACE) inhibitors, in that the angiotensin II blockers cause fewer side effects (most notably less cough and angioedema). Unlike ACE inhibitors, however, no data exist on the safety or efficacy of the angiotensin II blockers in the management of congestive heart failure or diabetic nephropathy. Of course, once an agent is approved by the US Food and Drug Administration, physicians have the authority to prescribe an agent for any indication that they feel appropriate for a given patient. We rely on the good judgment of physicians, and take comfort in the understanding that pharmaceutical manufacturers are prohibited from marketing their products for unapproved ("off label") indications. That may soon change.

Section 401 of the US Food and Drug Administration Modernization Act of 1997 provides pharmaceutical manufacturers with new latitude regarding the provision of information on off-label indications. The new law allows manufacturers to distribute published material on unapproved uses of approved agents after those materials have been reviewed by the FDA. Over the next 12 to 18 months, we should expect to see a substantial increase in off-label marketing as companies take advantage of this new regulation.

Critics of the new regulation suggest that by allowing the marketing of unapproved indications, there will be less incentive for pharmaceutical manufacturers to fund and conduct rigorous clinical trials in the pursuit of broader product labeling. Market competition may prevent a decrease in research - the only way for a manufacturer to find a unique niche for the sixth or seventh agent in a class will be to fund and conduct new trials. However, we should be concerned with the possible safety implications of off-label promotions, particularly during the first years after a prod-

uct is approved.

On June 8, 1998, Roche Laboratories announced the voluntary withdrawal of mibefradil (Posicor®) from the US market, less than one year after the Food and Drug Administration (FDA) approved the drug for the treatment of hypertension and chronic stable angina. Market withdrawal was precipitated by the failure of the product to demonstrate a difference in efficacy over placebo in a three-year congestive heart failure trial, and in response to concerns over the large number of potentially dangerous drug interactions noted with the product (particularly those between mibefradil and several lipid lowering agents in the HMG CoAg reductase inhibitor class). Two weeks later a newer NSAID, bromfenac (Duract®, Wyeth Ayerst), was removed from the market by its manufacturer due to concerns over reports of liver toxicity.

These two very recent examples not only provide support for diligent post-marketing surveillance of newly marketed medications, but also should raise concerns over pre-approval marketing. Would patient outcomes have suffered if Roche had been allowed to market mibefradil for CHF before the FDA had approved that indication? That would depend on whether physicians were influenced by the sales representatives. Are sales representatives generally effective? The answer to that question (from the perspective of the manufacturers themselves) is evident in the number of representatives in the field today.

As you consider the angiotensin II blockers, keep in mind that (unlike ACE inhibitors) no evidence exists supporting their use for indications other than hypertension. As always, please contact me at [lc.vermeulen@hosp.wisc.edu](mailto:lc.vermeulen@hosp.wisc.edu) with comments on this article or suggestions for future issues.

—Lee Vermeulen, MS, RPh

### Introduction

The role of the angiotensin system in the pathogenesis of hypertension is an active area of research. Angiotensin converting enzyme (ACE) inhibitors were the first class of drugs to target this system as a means of treating hypertension. The angiotensin receptor blockers (ARB) are a new class of medications which exert their antihypertensive

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effects by binding to the angiotensin I receptors. The marketed ARBs, which include valsartan (Diovan<sup>®</sup>, Novartis), losartan (Cozaar<sup>®</sup>, Merck), irbesartan (Avapro<sup>®</sup>, Bristol Myers Squibb), and eprosartan (Teveten<sup>®</sup>, Smith-Kline Beecham, approved but not yet available on market), appear to lower blood pressure as effectively as ACE inhibitors and demonstrate an adverse effect profile similar to that of placebo.

### Pharmacology

Angiotensin II is a potent vasoconstrictor which plays a significant role in the pathophysiology of hypertension. Angiotensin converting enzyme forms angiotensin II from angiotensin I. Binding of angiotensin II to angiotensin I receptors in the vasculature leads to an increase in the secretion of aldosterone, which promotes potassium excretion and sodium and water retention. This results in an increase in peripheral vascular resistance and, ultimately, an increase in blood pressure.

Angiotensin converting enzyme inhibitors work by inhibiting angiotensin converting enzyme, the enzyme responsible for the conversion of angiotensin I to angiotensin II. Angiotensin converting enzyme is also responsible for the metabolism of bradykinins, which are potent vasodilators. Angiotensin receptor blockers reduce blood pressure by selectively blocking the binding of angiotensin II to AT<sub>1</sub> receptors. Since the ARBs do not affect ACE they have limited impact on bradykinins and do not exhibit bradykinin-mediated side effects, such as cough and angioedema.<sup>1</sup>

### Pharmacokinetics

The time to peak effect ranges from 1 to 2 hours for the various ARBs.<sup>3-6</sup> Each has a half-life sufficiently long to allow for once or twice a day dosing. Losartan has an active metabolite; valsartan, irbesartan and eprosartan do not. Unlike valsartan and eprosartan, losartan and irbesartan are metabolized by cytochrome P450. See Table 1 for the kinetics of these agents.

### Clinical Trials

The clinical trials for these agents all employed a remarkably consistent study design. The studies were randomized, double-blind and parallel group trials utilizing similar inclusion and exclusion criteria and endpoints. Study eligibility was defined as mild to moderate, uncomplicated, essential hypertension with a mean sitting diastolic blood pressure (MSDBP) greater than or equal to 95 mmHg and less than or equal to 115 to 120 mmHg. Patients were excluded if they had a history of hypertensive encephalopathy or cerebrovascular accident, myocardial infarction in

the previous 3 months, heart failure in the previous 6 months, symptomatic heart failure, the presence of severe angina pectoris, significant valvular heart disease, malignant hypertension, second- or third-degree heart block or evidence of significant hepatic, renal or gastrointestinal disease. Patients were also excluded if any medication which would affect blood pressure was taken within 14 days of the randomization. Eligible patients were started in a minimum 1-week washout period during which all antihypertensive medications were discontinued. This washout period was typically followed by a 2-week lead-in phase during which patients were given placebo and assessed for the presence of essential hypertension. Patients who had measurable elevations of blood pressure at this point entered the treatment phase of the study.

### Valsartan

A study by Oprail et al was done to evaluate the efficacy and safety of valsartan compared to placebo in the treatment of essential hypertension.<sup>10</sup> Patients were stratified by age (<65 years and >65 years) and then randomized into one of five treatment groups. The patients received a once daily dose of valsartan 20, 80, 160 or 320 mg or placebo for 8 weeks. Blood pressures were measured by the same clinician at the start of the trial and at 4 and 8 weeks. Sitting blood pressure, standing blood pressure, pulse, body weight and clinical labs were monitored to evaluate valsartan safety and efficacy. Of the 738 patients enrolled in the trial, 668 patients completed the 8 week trial. Successful treatment was defined as a MSDBP less than 90 mmHg or a decrease of greater than 10 mmHg from baseline. Mean sitting diastolic blood pressure reduction was successful in 43%, 44% and 52% of the 80, 160 and 320 mg valsartan treatment groups, respectively ( $p < 0.001$ ). The response to valsartan 20 mg was no different than placebo. The most commonly reported side effects were headache and dizziness, with no significant differences between the placebo and valsartan groups.

Another study was conducted in Holland, Italy, and France to evaluate the safety and efficacy of valsartan compared to enalapril in the treatment of essential hypertension.<sup>11</sup> A total of 348 patients ranging from 20 to 79 years of age were randomized to take 80 mg of valsartan once daily, enalapril 20 mg once daily or placebo in a ratio of 2:2:1. Weight, heart rate, sitting systolic and diastolic blood pressure (SSBP and SDBP) and adverse events were recorded. Patients were instructed not to take their medication on the mornings of the week 4 and 8 office visits, so that the blood pressure measurement would reflect a true trough reading. Change in SDBP from baseline to the completion of the trial

was the primary variable used to evaluate the efficacy. Change in SSBP from baseline and response rates (percent of patients at the endpoint of SDBP <90 mmHg or a decrease in the SDBP  $\geq$ 10 mmHg from baseline) were assessed as secondary efficacy variables. The mean reduction in the SDBP was -9.5 mmHg for valsartan, -9.4 mmHg for enalapril, and -4.5 mmHg for placebo ( $p < 0.001$ ). The mean reduction in the SSBP was -12.4 mmHg, -13.1 mmHg and -5.7 mmHg for valsartan, enalapril and placebo ( $p < 0.003$ ), respectively. Valsartan had response rates of 48% for week 4, 55% for week 8, and 43% for both 4 and 8 weeks. Enalapril had similar response rates with 48% for week 4, 60% for week 8, and 45% for weeks 4 and 8 combined. The placebo group had a 9% response rate. The percent of patients which did not

respond to therapy with valsartan was 40% and enalapril was 37%, respectively. Cough was reported in 4.3% of patients for enalapril, 0.7% for valsartan and 0% for placebo.

Hegner et al enrolled 167 patients between the ages of 25 and 80 years old in a randomized, double-blind, comparative trial to evaluate the safety and efficacy of valsartan compared to hydrochlorothiazide.<sup>12</sup> This study had a secondary goal of assessing the efficacy and tolerability of valsartan in combination with atenolol 50 mg. Patients were randomized equally into two treatment groups, either the valsartan 80 mg once daily or the hydrochlorothiazide 25 mg once daily. Response to therapy was assessed at the end of 8 weeks. Atenolol 50 mg once daily was added to existing therapy in

Table 1. Pharmacokinetics for specific angiotensin receptor blockers

Kinetic Parameters	Valsartan <sup>3</sup>	Losartan <sup>4</sup>	Irbesartan <sup>5</sup>	Eprosartan <sup>6</sup>
Bioavailability	10-35%*	33%*	60-80%*	13%
Metabolism	minimal	liver	liver	Partially conjugated with glucuronic acid and excreted into bile and urine (NO CYP450 involvement)
	(CYP 3A4 and 2C9)	(mainly CYP 2C9)	glucuronic acid and excreted into bile and urine (NO CYP450 involvement)	
Metabolites	inactive	active	inactive	inactive
Peak effect ( $T_{max}$ )	2-4 hrs 3-4 hrs (metabolite)	1 hr (losartan)	2 hrs	2-4 hrs <sup>7,8</sup>
Half life ( $t_{1/2}$ )	6 hrs 6-9 hrs (metabolite)	2 hrs (losartan)	11-15 hrs	5-9 hrs
Volume of distribution (Vd)	17 L	34L losartan 12L active metabolite	53-93 L	308 L
Elimination	71% feces, 10% urine	60% feces , 35% urine (losartan) 55% feces , 45% urine (metabolite)	80% feces, 20% urine	90% feces, 7% urine <sup>6,9</sup>
Protein binding	95%	99.3% (losartan) 99.8% (metabolite)	90%	98% <sup>6,7</sup>

\*There is a 50% reduction in absorption if valsartan is taken with food. There is a 10% reduction in absorption for losartan when taken with food that is clinically insignificant. No reduction in absorption was observed for irbesartan. The absorption of eprosartan is delayed when taken with food. The area under the curve (AUC) values increase by approximately 25%, but this is clinically insignificant.<sup>6</sup>

any patients who continued to have a SDBP greater than or equal to 95 mmHg. Atenolol was needed in 16 (20%) patients in the valsartan group and 17 (20%) from the hydrochlorothiazide group. All patients were evaluated again at the end of 12 weeks. The change in mean SDBP was similar in both groups at the 8 and 12 week assessments. The mean change in SDBP at 8 weeks was -13.6 mmHg for valsartan and -12.0 mmHg for hydrochlorothiazide. The corresponding changes at 12 weeks were -15.3 mmHg for valsartan and -14.3 mmHg for hydrochlorothiazide. The mean change in SSBP was -16.6 mmHg and -18.6 mmHg for the valsartan group at weeks 8 and 12, respectively. The mean changes in SSBP for hydrochlorothiazide were -18.5 mmHg at 8 weeks and -20.3 mmHg at 12 weeks. None of these differences were statistically significant. The number of patients who reported adverse events were similar in the two regimens, five with valsartan and seven with hydrochlorothiazide.

Another study enrolled 168 patients between the ages of 18 and 80 years old in a trial to compare the efficacy and safety of valsartan vs amlodipine in the treatment of essential hypertension.<sup>13</sup> Patients were randomized to receive 80 mg of valsartan once daily or 5 mg of amlodipine once daily. At the end of 8 weeks, patients in both treatment arms with a SDBP greater than or equal to 95 mmHg were also given a daily dose of 5 mg of amlodipine. Blood pressure control was evaluated at the end of 12 weeks to assess the efficacy of each regimen. The reduction in SDBP at weeks 8 and 12 was -11.5 mmHg and -13.5 mmHg for valsartan and -11.1 mmHg and -14.2 mmHg for amlodipine. There was a reduction in SSBP of -13.1 mmHg and -16.5 mmHg for valsartan and a reduction of -14.8 mmHg and -19.3 mmHg for amlodipine in weeks 8 and 12. Valsartan had a 66.7% response rate compared to a 60.2% response rate for amlodipine. These results were not statistically significant.

### Losartan

A pair of multicenter clinical trials were conducted to evaluate the efficacy, tolerability and quality of life for losartan, either alone or in combination with hydrochlorothiazide, compared to amlodipine or nifedipine in patients with essential hypertension. Patients were required to fill out a quality of life questionnaire and to stop taking any antihypertensive medication before they started a 4-week placebo run-in period. The questionnaire assessed quality of life by asking patients to examine seven different areas which included: cognitive functioning, social functioning, psychological well-being, sleep disturbances, sexual functioning, symptom bother and overall health perceptions. Patients were stratified into two groups; group one had a

SDBP greater than or equal to 95 mmHg and less than or equal to 105 mmHg and group two had a SDBP greater than or equal to 106 mmHg and less than or equal to 115 mmHg. The patients in each stratum were then randomized into one of two study groups for 12 weeks of active treatment. The study groups were evaluated every 4 weeks during the treatment period to record the vital signs, adverse events, and quality of life measurements. Blood pressure was considered to be controlled if the SDBP was less than 90 mmHg. In patients whose hypertension was not controlled dose titration was done according to specific protocols at weeks 4 and 8. A follow-up examination was done at the end of the 16 weeks to measure the outcome of the treatment. The primary goal of the therapy was to reduce SDBP below 90 mmHg. If the patients did not reach the primary goal, they were evaluated for a secondary endpoint which was at least a 10 mmHg reduction in the SDBP.

The first trial compared losartan to amlodipine in the treatment of essential hypertension.<sup>14</sup> Patients were started on either losartan 50 mg or amlodipine 5 mg once daily. If the SDBP was not adequately controlled after 4 weeks of therapy, the regimen was adjusted to either losartan 50 mg plus 12.5 mg of hydrochlorothiazide once daily or amlodipine 10 mg once daily. After 8 weeks, if blood pressures were still uncontrolled, hydrochlorothiazide 25 mg was added to each regimen. At weeks 4, 8 and 12 there was a 7.3 mmHg, 10.4 mmHg and 11.1 mmHg reduction in SDBP from baseline in the losartan treatment group compared to a 7.9 mmHg, 11.2 mmHg and 11.8 mmHg reduction for amlodipine. The initial treatment regimen controlled blood pressure in 33% of the losartan patients and 37% of the amlodipine patients. The addition of 12.5 mg and 25 mg of hydrochlorothiazide controlled blood pressure in 28% and 39% of the patients in the losartan group. In comparison, 32% and 31% of the patients were controlled on amlodipine 10 mg once daily and amlodipine 10 mg plus 25 mg of hydrochlorothiazide once daily. The percent of patients achieving the goal of SDBP less than 90 mmHg were 53% and 51% for losartan and amlodipine, respectively [ $p$ = not significant (ns)]. The total percent of adverse experiences was comparable between the two groups (losartan 63% vs. 68% amlodipine). However, there was a greater incidence of edema (14% vs 2%; $p=0.003$ ) and drug-related edema (11% vs 1%; $p=0.004$ ) for amlodipine compared to losartan. The quality of life assessments were comparable for losartan and amlodipine, except for patients bothered by edema, where the incidence was 12% vs 2% for amlodipine and losartan respectively ( $p=0.01$ ).

The second study enrolled 223 patients in a multicenter trial to compare the efficacy, tolerability and quality of life for losartan vs nifedipine.<sup>15</sup> Patients were randomized to

treatment groups of either losartan 50 mg or nifedipine extended release tablets 30 mg once daily. If blood pressure was not controlled after 4 weeks of treatment, either hydrochlorothiazide 12.5 mg daily was added to the losartan regimen or the nifedipine dose was increased to 60 mg once daily. If blood pressure was still not adequately controlled after another 4 weeks, the hydrochlorothiazide dose was increased to 25 mg once daily and the nifedipine dose was increased to 90 mg once daily. The mean reduction in the SDBP was similar between the two groups at weeks 4, 8, and 12 (losartan: 8.9 mmHg, 11.6 mmHg and 12.7 mmHg vs nifedipine: 9.3 mmHg, 11.0 mmHg and 11.1 mmHg). The percent of patients who reached a SDBP of less than 90 mmHg was similar with 59% of the losartan patients and 54% of the nifedipine patients reaching the primary goal ( $p=ns$ ). Edema was more common with nifedipine than losartan (12% vs 3%;  $p=0.007$ ). The presence of edema was a significant quality of life issue. Edema was reported to have a negative impact on the quality of life in 27% of patients taking nifedipine and 9% of patients taking losartan ( $p=0.004$ ).

A 16 week study enrolled 122 nonblack patients with mild to moderate hypertension to assess the effects of losartan on blood pressure.<sup>16</sup> After completion of the 4-week run-in period patients were placed into one of the following treatment groups: losartan 50 mg once daily, losartan 50 mg twice daily, losartan 100 mg once daily or placebo. If blood pressure was not controlled after 4 weeks of monotherapy, either hydrochlorothiazide 12.5 mg or placebo was added. The reduction in the SSBP from baseline was 9.2 mmHg, 9.9 mmHg, 13.2 mmHg and 0.0 mmHg for the losartan 50 mg once daily, 100 mg once daily, 50 mg twice daily and placebo groups, respectively ( $p<0.01$ ). The difference between losartan 50 mg twice daily and losartan 100 mg once daily was statistically significant ( $p<0.05$ ). The reduction in SDBP was similar with 5.2 mmHg, 6.4 mmHg, 8.5 mmHg and 0.2 mmHg for losartan 50 mg once daily, 100 mg once daily, 50 mg twice daily and placebo, respectively ( $p<0.01$ ). A significant reduction in SDBP was observed for losartan 50 mg twice daily compared to 100 mg once daily ( $p<0.05$ ). The addition of hydrochlorothiazide caused similar decreases in blood pressure in each group ( $p=ns$ ).

Losartan and low-dose hydrochlorothiazide were evaluated in a 16-week trials in 703 adult patients with essential hypertension.<sup>17</sup> After a 4-week placebo run-in period, followed by a 12-week double-blinded trial where patients were randomized and stratified into a treatment group of losartan 50 mg once daily, hydrochlorothiazide 12.5 mg once daily, losartan 50 mg and hydrochlorothiazide 6.25 mg once daily, losartan 50 mg and hydrochlorothiazide 12.5 mg

once daily, or placebo. Patients were stratified by degree of hypertension ( mild, 95-105 mmHg and moderate, 106-115 mmHg) and by race (nonblack vs black). Patients were seen every 3 weeks during the treatment period to monitor SDBP. After 12 weeks of treatment, the changes in trough SDBP from baseline were -4.1 mmHg for placebo, -7.2 mmHg for HCTZ 12.5 mg, -8.8 mmHg for losartan 50 mg, -9.3 mmHg for losartan 50 mg/HCTZ 6.25 mg and -13.2 for losartan 50 mg/HCTZ 12.5 mg. The changes in SSBP were -2.0 mmHg for placebo, -9.2 mmHg for HCTZ 12.5 mg, -10.7 mmHg for losartan 50 mg, -11.7 mmHg for losartan 50 mg/HCTZ 6.25 mg and -17.2 for losartan 50 mg/HCTZ 12.5 mg. The reduction in SDBP and SSBP for losartan 50 mg/HCTZ 12.5 mg was significantly greater compared to the other groups ( $p\leq 0.001$ ). Also, a statistically significant reduction in SDBP was observed for losartan 50 mg vs HCTZ 12.5 mg ( $p=0.05$ ).

Another 12-week trial was conducted to evaluate the safety and efficacy of losartan as an adjunct medication for patients whose blood pressure was uncontrolled on 25 mg of hydrochlorothiazide once daily.<sup>18</sup> The 304 patients were randomized into one of four groups: HCTZ 25 mg alone or HCTZ 25 mg 25, 50 or 100 mg of losartan once daily for 12 weeks. Office visits were conducted during weeks 1, 3, 6, 9 and 12 to evaluate therapy and to monitor for any adverse experiences. The mean reduction in SSBP was -3.6 for HCTZ 25 mg, -10.0 for losartan 25 mg/HCTZ, -12.6 for losartan 50 mg/HCTZ and -16.2 for losartan 100 mg. The mean reduction in SDBP was -6.7 for HCTZ 25 mg, -9.6 for losartan 25 mg/HCTZ, -12.0 for losartan 50 mg/HCTZ and -13.3 for losartan 100 mg. All patients in the losartan/HCTZ groups had statistically significant reductions in SSBP and SDBP compared to monotherapy with HCTZ ( $p<0.01$ ).

Gradman and associates conducted a multicenter trial to compare losartan to enalapril in the treatment of essential hypertension.<sup>19</sup> There were seven treatment groups: losartan 10 mg, 25 mg, 50 mg, 100 mg or 150 mg once daily, enalapril 20 mg once daily or placebo. The reduction of SDBP from baseline was -7.3 mmHg, -9.9 mmHg, -11.9 mmHg, -10.4 mmHg and -13.1 mmHg for losartan 10 mg, 25 mg, 50 mg, 100 mg, and 150 mg respectively. In the enalapril patients the mean reduction in SDBP from baseline was -16.2 mmHg. These changes were all statistically significant ( $p<0.01$ , except for the 150 mg group which was significant at  $p<0.05$ ). The incidence of cough was greater in the enalapril group than in the losartan group (8 vs 3%).

Pitt and associates conducted a prospective double-blind, randomized, clinical trial to evaluate losartan vs captopril in the treatment of heart failure in elderly patients (ELITE trial).<sup>20</sup> Patients were 65 years or older with symptomatic heart failure, an ejection fraction of 40% or less and no

history of previous ACE inhibitor therapy. Following a 2-week placebo lead-in period, 722 patients were randomized to 48 weeks of treatment with either captopril 50 mg three times daily or losartan 50 mg once daily. Death and/or hospitalization due to heart failure occurred in 9.4% of the losartan patients and 13.2% of the captopril patients ( $p=ns$ ). The number of admissions due to heart failure were comparable in both groups, as was improvement in functional status.

Chang conducted a small double-blind, clinical trial in 12 patients to investigate the effect of losartan on left ventricular hypertrophy.<sup>21</sup> Following a one-week lead-in period, patients with left ventricular hypertrophy and untreated mild hypertension were randomized to treatment with losartan or placebo. Echocardiography was used to assess left ventricular mass at baseline and after 12 weeks of treatment. Patients treated with losartan had a statistically significant increase in left ventricular mass ( $19.3 \text{ g/m}^2$ ,  $p=0.01$ ). In the placebo recipients, left ventricular mass increased from  $107.8 \text{ g/m}^2$  to  $108.9 \text{ g/m}^2$  ( $p=ns$ ). The author concluded that the different mechanisms of action may explain the differing effects of ARBs and ACE inhibitors on left ventricular mass. Both losartan and placebo had similar effects on blood pressure.

### Irbesartan

A randomized, double-blind, placebo-controlled matrix study evaluated irbesartan in combination with hydrochlorothiazide for the treatment of mild to moderate hypertension.<sup>22</sup> Patients were enrolled in a 4 to 5 week lead-in period to establish the presence of hypertension (SDBP 95 to 110 mmHg). Patients were placed in one of 16 possible treatment regimens. The regimens were derived from combinations of varying doses of irbesartan (37.5 mg, 100 mg, 300 mg or placebo) and hydrochlorothiazide (6.25 mg, 12.5 mg, 25 mg or placebo). Patients were placed on the specific treatment arm of the study for 8 weeks. This study reported a dose-related increase in response up to 300 mg of irbesartan where the reduction in SDBP seemed to plateau.

Another multicenter, randomized, double-blind, parallel group trial compared irbesartan and enalapril in the treatment of mild to moderate hypertension.<sup>23</sup> Patients were randomized to receive either enalapril 10 mg, 20 mg or 40 mg once daily or irbesartan 75 mg, 150 mg or 300 mg once daily. The reductions in SDBP were comparable between the enalapril and irbesartan treatment groups. The only difference observed between the two groups was the incidence of cough (17% enalapril vs 10% irbesartan;  $p<0.001$ ).

Another randomized, multicenter, double-blind, parallel study was conducted to compare irbesartan and enalapril in the treatment of severe hypertension over a 12-week

period.<sup>24</sup> Patients, who had a mean SDBP of 115 to 130 mmHg were randomized in a 2:1 ratio to receive irbesartan 150 mg once daily or enalapril 20 mg once daily. If SDBP was still greater than 105 mmHg during week one or 90 mmHg during week 2, the doses were increased to a maximum of irbesartan 300 mg or enalapril 40 mg per day. If the SDBP was still greater than 90 mmHg, open label use of hydrochlorothiazide 25 to 50 mg per day, long-acting nifedipine 30 to 60 mg per day or atenolol 50 to 100 mg per day was allowed for the remainder of the study. Both the number of patients controlled on monotherapy and the number of patients requiring adjunct medicines were comparable in the two groups. The reduction in SDBP from baseline was -34.2 and -34.4 mmHg for enalapril and irbesartan, respectively. Cough was noted in 13% of the enalapril group compared to 2.5% of the irbesartan group ( $p=0.007$ ).

### Eprosartan

Eprosartan was approved by the Food and Drug Administration (FDA) in December 1997 for the treatment of hypertension.<sup>25</sup> At the time of this writing, the manufacturer and the FDA are engaged in ongoing discussions regarding product labeling. There are no published clinical trials evaluating the effect of eprosartan in the treatment of hypertension.

### Candesartan

Candesartan (Atacand®, Astra Merck) was approved by the FDA in June 1998.<sup>26</sup> As with eprosartan, there are no published clinical trials of candesartan.

### Adverse Effects

#### Cough

One of the most bothersome side effects of the ACE inhibitors is a dry, persistent cough. This cough occurs in 5 to 20% of patients and often results in discontinuation of the ACE inhibitor.<sup>27</sup> The mechanism of this cough is not truly understood, but is thought to be bradykinin-mediated. ARBs are not expected to cause cough, since they have not been shown to have any effect on ACE. There have been several studies which have examined the incidence of cough associated with ARBs.

In a multicenter, double-blind, randomized, active-controlled, parallel group trial, Benz and associates followed patients for 12 to 16 weeks to observe the incidence of cough in patients receiving valsartan compared to lisinopril and hydrochlorothiazide.<sup>28</sup> A total of 132 patients with a history of ACE inhibitor-induced cough participated in the study. Patients were evaluated before and after each phase of the trial and during weeks 3 and 6 of the active arm of the study.

The combined incidence of cough for weeks 3 and 6 was 19.5%, 68.9% and 19.0% for valsartan, lisinopril and hydrochlorothiazide respectively. The difference in incidence of dry cough between valsartan and lisinopril was -49.4% ( $p < 0.001$ ). The difference between hydrochlorothiazide and lisinopril was -49.9% ( $p < 0.001$ ).

A ten-week, double-blind, parallel group study was conducted to compare losartan, lisinopril and metolazone in elderly patients with previous ACE inhibitor induced cough.<sup>29</sup> Patients were assessed every 2 weeks during the ten-week active portion of the study. The incidence of cough was greater for lisinopril compared to losartan, 97% vs 18% ( $p < 0.001$ ). The incidence of cough was similar between losartan and metolazone, 18% vs 21% ( $p < 0.001$ ).

### Angioedema

Angioedema is reported in 0.1 to 0.2% of patients receiving ACE inhibitors.<sup>30</sup> The vasodilator effects of bradykinin are responsible for the development of angioedema. Theoretically, since the ARBs have no effect on bradykinins, angioedema should not be a concern with these agents. However, there has been one case report of angioedema in a patient taking losartan.<sup>31</sup> Facial edema has also occurred in several patients taking eprosartan.<sup>10</sup>

### Cost, Dose, How Supplied

The usual dose of valsartan is 80 to 160 mg once daily for the treatment of hypertension. The average wholesale price (AWP) for 80 and 160 mg valsartan capsules is \$117.00 for 100 capsules. The usual dose of losartan is 50 mg once daily. In volume depleted patients, the recommended starting dose is 25 mg once daily. The total dose of losartan can be divided and taken twice daily if needed to achieve better response. Losartan is available in 25 mg and 50 mg tablets. The average wholesale price (AWP) for 25 and 50 mg tablets is \$110.00 for 100 tablets. The usual dose of irbesartan is 150 mg once daily for the treatment of hypertension. In volume- and salt-depleted patients, the recommend starting dose is 75 mg once daily. Cost data was not available at the time of writing for eprosartan and candesartan. The ARBs do not require any initial dose adjustments for elderly patients or patients with mild-to-moderate renal or liver insufficiency. Addition of a diuretic has a greater effect on blood pressure than does increasing the dose of the ARB.

### Conclusion

Angiotensin receptor blockers are indicated for use in hypertension either alone or in combination with other

antihypertensive agents. The ARBs have been shown to have a decreased incidence of cough and angioedema compared to ACE inhibitors. In clinical trials, ARBs were similar to placebo with respect to rates of cough and angioedema. Currently, there are five approved ARBs valsartan, losartan, irbesartan, eprosartan and candesartan.<sup>38,39</sup> Neither eprosartan nor candesartan will be marketed until sometime in 1998.

Angiotensin converting enzyme inhibitors are beneficial in the treatment of hypertension, congestive heart failure (CHF) and diabetic nephropathy. While ARBs have consistently been shown to be as effective as ACE inhibitors in reducing blood pressure, there is limited information on their role in the management of CHF and diabetic nephropathy. The ELITE trial found losartan and captopril produced similar improvements in NYHA heart failure classification, but further study is needed before routinely recommending ARBs as alternatives to ACE inhibitors in the treatment of CHF. No studies examining the role of ARBs in diabetic nephropathy were identified. At this time, the primary use for ARBs are as an alternative to ACE inhibitors in patients experiencing angioedema or cough. Clinical trials have shown that all of the ARBs have similar antihypertensive effects and similar side effect profiles. In the absence of clinical differences, formulary decisions about ARBs can be made on the basis of cost alone. ■

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