ANTIHYPERTENSIVE DRUGS

Drugs used in the management of primary hypertension belong to several different groups, including angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), also called angiotensin II receptor antagonists (AIIRAs), antiadrenergics, calcium channel blockers, diuretics, and direct vasodilators. In general, these drugs act to decrease blood pressure by decreasing cardiac output or peripheral vascular resistance.

Angiotensin-Converting Enzyme Inhibitors

Angiotensin-converting enzyme (also called kininase) is mainly located in the endothelial lining of blood vessels, which is the site of production of most angiotensin II. This same enzyme also metabolizes bradykinin, an endogenous substance with strong vasodilating properties.

ACE inhibitors block the enzyme that normally converts angiotensin I to the potent vasoconstrictor angiotensin II. By blocking production of angiotensin II, the drugs decrease vasoconstriction (having a vasodilating effect) and decrease aldosterone production (reducing retention of sodium and water). In addition to inhibiting formation of angiotensin II, the drugs also inhibit the breakdown of bradykinin, prolonging its vasodilating effects. These effects and possibly others help to prevent or reverse the remodeling of heart muscle and blood vessel walls that impairs cardiovascular function and exacerbates cardiovascular disease processes. Because of their effectiveness in hypertension and beneficial effects on the heart, blood vessels, and kidneys, these drugs are increasing in importance, number, and use. Widely used to treat heart failure and hypertension, the drugs may also decrease morbidity and mortality in other cardiovascular disorders. They improve post–myocardial infarction survival when added to standard therapy of aspirin, a beta blocker, and a thrombolytic.

ACE inhibitors may be used alone or in combination with other antihypertensive agents, such as thiazide diuretics. Although the drugs can cause or aggravate proteinuria and renal damage in nondiabetic people, they decrease proteinuria and slow the development of nephropathy in diabetic clients.

Most ACE inhibitors (captopril, enalapril, fosinopril, lisinopril, ramipril, and quinapril) also are used in the management of heart failure because they decrease peripheral vascular resistance, cardiac workload, and ventricular remodeling. **Captopril** and other ACE inhibitors are recommended as first-line agents for treating hypertension in diabetic clients, particularly those with type 1 diabetes and/or diabetic nephropathy, because they reduce proteinuria and slow progression of renal impairment.

ACE inhibitors are well absorbed with oral administration, produce effects within 1 hour that last approximately 24 hours, have prolonged serum half-lives with impaired renal function, and most are metabolized to active metabolites that are excreted in urine and feces. These drugs are well tolerated, with a low incidence of serious adverse effects (eg, neutropenia, agranulocytosis, proteinuria, glomerulonephritis, and angioedema). However, a persistent cough develops in approximately 10% to 20% of clients and may lead to stopping the drug. Also, acute hypotension may occur when an ACE inhibitor is started, especially in clients with fluid volume deficit. This reaction may be prevented by starting with a low dose, taken at bedtime, or by stopping diuretics and reducing dosage of other antihypertensive drugs temporarily. Hyperkalemia may develop in clients who have diabetes mellitus or renal impairment or who are taking nonsteroidal anti-inflammatory drugs, potassium supplements, or potassium-sparing diuretics.

These drugs are contraindicated during pregnancy because serious illnesses, including renal failure, have occurred in neonates whose mothers took an ACE inhibitor during the second and third trimesters.

Angiotensin II Receptor Blockers

Angiotensin II receptor blockers (ARBs) were developed to block the strong blood pressure–raising effects of angiotensin II. Instead of decreasing production of angiotensin II, as the ACE inhibitors do, these drugs compete with angiotensin II for tissue binding sites and prevent angiotensin II from combining with its receptors in body tissues. Although multiple types of receptors have been identified, the AT1 receptors located in brain, renal, myocardial, vascular, and adrenal tissue determine most of the effects of angiotensin II on cardiovascular and renal functions. ARBs block the angiotensin II AT1 receptors and decrease arterial blood pressure by decreasing systemic vascular resistance (Fig. 55–1).

These drugs are similar to ACE inhibitors in their effects on blood pressure and hemodynamics and are as effective as ACE inhibitors in the management of hypertension and probably heart failure. They are less likely to cause hyperkalemia than ACE inhibitors, and the occurrence of a persistent cough is rare. Overall, the drugs are well tolerated, and the incidence of most adverse effects is similar to that of placebo.

Losartan, the first ARB, is readily absorbed and rapidly metabolized by the cytochrome P450 liver enzymes to an active metabolite. Both losartan and the metabolite are highly bound to plasma albumin, and losartan has a shorter duration of action than its metabolite. When losartan therapy is started, maximal effects on blood pressure usually occur within 3 to 6 weeks. If losartan alone does not control blood pressure, a low dose of a diuretic may be added. A combination product of losartan and hydrochlorothiazide is available.

Antiadrenergics

Antiadrenergic (sympatholytic) drugs inhibit activity of the SNS. When the SNS is stimulated (see Chap. 17), the nerve impulse travels from the brain and spinal cord to the ganglia. From the ganglia, the impulse travels along postganglionic fibers to effector organs (eg, heart, blood vessels). Although