REVIEWS IN MEDICINE ALAN SUGAR, EDITOR

Contemporary Antihypertensive Therapy

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Abstract. Pharmacotherapy of human hypertension is effective, safe and well-tolerated. Antihypertensive drugs are of three broad classes: diuretics, sympatholytics and vasodilators. The use of each class is discussed and a summary of therapeutic considerations offered for representative agents. Recent trends in antihypertensive therapy are identified. (**Surv Ophthalmol 32:** 178–188, 1987)

Three decades of progress in the therapy of human hypertension, fueled by a steady flow of novel pharmacologic agents, have established contemporary pharmacotherapy as broadly effective, safe, and acceptable to patients. Although the selection of specific regimens for individual patients remains a trial-and-error process, the wide range of currently available drugs virtually ensures that skilled clinicians will be able to reduce blood pressure to desired levels in all patients. However, as the number of choices increases, so does the complexity of their application, and many today approach the antihypertensive pharmacopoea with trepidation. This review attempts to provide an overview of the currently available pharmaceuticals, limited to those used in chronic oral therapy, and a description of strategies for their use in contemporary practice.

I. Oral Agents Marketed for Antihypertensive Therapy

Available agents are summarized in Table 1. The following comments expand on some of the advantages and potential drawbacks of specific classes.

A. DIURETICS

Diuretics formed the basis of our original "stepped-care" therapy and continue to be the most widely used drugs worldwide. Despite possible disadvantages related to physiological and biochemical side-effects, it must be conceded that diuretics remain remarkably efficacious, affordable, and generally well-tolerated. All the major trials assessing the efficacy of antihypertensive therapy in reducing cardiovascular morbidity and mortality have included a diuretic treatment limb, and no other class of drugs has ever been demonstrated to be superior to diuretics in reducing all-cause mortality. Concerns about the use of diuretics as initial therapy have centered about two issues: 1) the provocation of biochemical side-effects which may be related to adverse outcomes; and 2) the relatively high incidence of subjective side-effects which limit patient acceptance.

Diuretic agents (thiazides, "loop" and indoline) lower blood pressure in hypertensive patients by impairing renal tubular sodium reabsorption through the inhibition of site-specific luminal mem-

TABLE 1

Oral Agents Used in Antihypertensive Therapy

Generic Name	Trade Name(s) (*combination drug)	Schedules‡ (mg/day)	Side Effects
I. DIURETICS			
A. Thiazide and thiazide-like			Side effects are similar for the entire class of thiazide diuretics.
Bendroflumethiazide	Naturetin Rauzide*	ID 1× 2.5–5.0 DR 2.5–10 MD 1× 5–10	Hypokalemia, hyperuricemia, hypo-magnesemia, hypercalcemia, azo-temia, muscle cramps, weakness, arrhythmias, dizziness, glucose intolerance, impotence.
Benzthiazide	Aquatag Aquex Exna Hydrex	ID 1× 25 DR 25 – 100 MD 1× 25–100	Hypercholesterolemia (increased to-tal, decreased HDL, hypertriglyc-eridemia.
Chlorothiazide	Aldoclor* Diupres* Diuril	ID 1× 250 DR 250–1000 MD 1–2× 250–1000	
Chlorthalidone	Combipres* Hygroton Regroton*	ID 1× 25 DR 25–100 MD 1× 25–100	
Cyclothiazide	Anhydron	ID 1× 1 DR 1–4 MD 1× 2–4	
Hydrochlorothiazide	Aldactazide* Aldoril* Apresazide* Dyazide* Esidrix Esimil* Hydrodiuril Hydropres* Inderide* Maxzide* Oretic Oreticyl* Ser-AP-Es* Uropres*	ID 1× 25 DR 25–50 MD 25–50	Hypercholesterolemia (increased total, decreased HDL), hyper-triglyceridemia
Hydroflumethiazide	Diucardin Saluron Salutensin*	ID 1× 25 DR 25–50 MD 1–2× 25–50	
Methyclothiazide	Aquatensen Diutensin* Dutron* Endoron Endoronyl*	ID 1× 25 DR 2.5–5 MD 1× 2.5–5	
Metolazone	Diulo Zaroxolyn	ID 1× 2.5–10 DR 2.5–10 MD 1–2× 2.5–10	
Polythiazide	Minizide* Renese Renese-R	ID 1× 1 DR 1–4 MD 1× 1–4	
Quinethazone	Hydromax	ID 1× 25 DR 25–100 MD 1–2× 25–50	
Trichlormethiazide	Metahydrin Metatensin* Naqua Naquival* Ropres*	ID 1× 2 DR 2–4 MD 1× 2–4	
B. Loop Diuretics			
Bumetamide	Bumex	ID 1× 0.5 DR 1–8	Group side effects: Similar to thia-zide except that these agents pro-

TABLE 1

(Continued)

Generic Name	Trade Name(s) (*combination drug)	Schedules‡ (mg/day)	Side Effects
		MD 2× 1–4	mote calciuria and lower blood levels of calcium.
Ethacrynic acid	Edecrin	ID 2× 25 DR 50–200 MD 2× 25–100	
Furosemide	Lasix	ID 2× 20 DR 20–480 MD 2× 20–240	
C. Potassium sparing Amiloride	Moduretic* Midamor	ID 1× 5 DR 5–40 MD–2× 5–20	Group side effects: hyperkalemia, hypokalemia, (with Moduretic) hyponatremia, dyspepsia.
Spironolactone	Aldactone Aldactazide*	ID 1× 50 DR 50–200 MD 1–2× 50–200	Gynecomastia, mastodynia, menstrual irregularities, impotence.
Triamterene	Dyazide* Dyrenium Maxzide*	ID 1× 50 DR 50–200 MD 1–2× 50–100	Gastrointestinal disturbances, macrocytic anemia.
D. Inodoline Indapamide	Lozol	ID 2.5 DR 2.5–5 MD 1× 2.5–5	Hypokalemia, hyperuricemia, dyspepsia.
II. SYMPATHOLYTICS			
A. Central nervous system Clonidine	Catapres Catapres TTS Combipres*	ID 2× 0.05 DR 0.1–1.2 MD 2–3× 0.1–0.4	Sedation, dry mouth, constipation, postural hypotension, male impotence, urinary retention, weight gain, increased effect of alcohol, withdrawal (rebound) hypertension.
Guanabenz	Wytensin	ID 2.4 DR 8–32 MD 2× 4–16	Same as clonidine.
Methyldopa	Aldoclor* Aldomet Aldoril*	ID 2–3× 250 DR 100–2000 MD 2× 250–1000	Sedation, dizziness, dry mouth, headache, gastro-intestinal disturbances, orthostatic hypotension, decreased libido, positive Coomb's test rarely with hemolytic anemia, fever, liver dysfunction rarely with intrahepatic cholestasis and granulomas.
Reserpine & related agents	Chlorserpine* Diupres* Diutensen* H-H-R tablets* Harmonyl Hydromox®* Hydropres* Metatensin* Moderil Naquival* Randixin Regroton* Renese-R* Ropres* Salutensin* Ser-Ap-Es* Serpasil* Unipres*	ID 1× 0.1 (as reserpine) MD 1× 0.1–1.0 DR 0.1–1.0	Drowsiness, sedation, nasal congestion, nightmares, depression, lethargy, weakness, nausea, vomiting, diarrhea, abdominal cramps, peptic ulcer, extrapyramidal side effects (Parkinson syndrome).

TABLE 1

(Continued)

Generic Name	Trade Name(s) (*combination drug)	Schedules‡ (mg/day)	Side Effects
B. Peripheral nervous system			
1. Post-ganglionic Neurons			
Guanadrel	Hylorel	ID 2× 5 DR 10–80 MD 2× 5–40	Postural hypotension, failure of ejaculation, impotence, diarrhea, muscular weakness, nasal stuffiness, bradycardia, weight gain, congestive heart failure.
Guanethidine	Esimil* Ismelin	ID 1× 10 (or load w/80) DR 10–100 MD 1× 25–50	Same as guanadrel.
2. Post-junctional receptor blockers			
a) *Alpha Adrenergic Blockers*			
Phenoxybenzamine	Dibenzyline	ID 2× 10 DR 20–60 MD 2–3× 10–20	Nasal congestion, postural hypotension, tachycardia, inhibition of ejaculation, mental clouding and drowsiness.
Prazosin	Minipres Minizide*	ID 2–3× 1 DR 1–30 MD 2–3× 10	Orthostatic hypotension (first dose effect), headache, drowsiness, weakness, palpitations, dry mouth, nasal congestion.
Terazosin	Hytrin	ID 1× 1 DR 1–20 MD 1× 1–30	Same as prazosin.
b) *Beta Adrenergic Blockers*			
Acebutalol	Sectral	ID 1× 200–400 DR 200–400 MD 1× 200–400	Group side effects: nausea, vomiting, anorexia, dizziness-bradycardia (less pronounced under beta-blockers with intrinsic,
Atenolol	Tenormin Tenoretic*	ID 1× 25–50 DR 50–100 MD 2× 25–200	sympathomimetic activity). Confusion, vivid dreams, nightmares, insomnia, depression.
Metoprolol	Lopressor	ID 2× 25–50 DR 50–400 MD 2× 25–200	
Nadolol	Corgard Corzide*	ID 1× 40–80 DR 40–240 MD 1× 40–240	Aggravation of existing impairment of myocardial contractility or of conduction through AV node.
Pindolol	Visken	ID 2× 5–10 DR 10–30 MD 2× 5–15	Respiratory distress or asthmatic attacks in patients with chronic bronchitis, emphysema, and
Propranolol	Inderal	ID 2× 20–40 DR 40–480 MD 2× 20–240	asthma through blockade of bronchial beta$_2$ blockers, probably less pronounced under
	Inderal LA	ID 1× 80 DR 80–480 MD 1× 80–480	beta blockers with intrinsic sympathomimetic activity). Hypoglycemia (blockade of glycy-
Timolol	Blocadren Timolide*	ID 2× 5–10 DR 10–30 MD 2× 5–15	genolytic and lipolytic action of catecholamines). Peripheral arterial insufficiency, intermittent claudication, Raynaud's phenomenon (through blockade of vasodilator beta$_2$-receptors). Exacerbation of coronary insufficiency after abrupt withdrawal of beta-blocker treatment in patients with coronary heart disease.
c) *Alpha and Beta Adrenergic Blocker*			
Labetalol	Normodyne Trandate	ID 2× 100–200 DR 200–1200 MD 2–3× 100–400	Postural hypotension, dizziness, gastrointestinal symptoms, bronchoconstriction, depression, lethargy, headache.

TABLE 1

(Continued)

Generic Name	Trade Name(s) (*combination drug)	Schedules‡ (mg/day)	Side Effects
III. VASODILATORS			
A. Vascular smooth muscle relaxants			
Hydralazine	Apresoline Apresazide* Hydrap-Es* Ser-Ap-Es* Unipres*	ID 2 × 25 DR 50–300 MD 2–3 × 25–100	Palpitations, tachycardia, headaches, edema.
Minoxidil	Loniten	ID 2 × 2.5 DR 2.5–40 MD 2 × 2.5–20	Hirsutism, fluid retention, palpitations, tachycardia.
B. Angiotensin converting enzyme inhibitors			
Captopril	Capoten Capozide	ID 2 × 12.5 DR 25–300 MD 2–3 × 12.5–100	Dysgeusia, rash, leukopenia, proteinuria, hypotension, cough.
Enalapril	Vasotec	ID 1 × 5 DR 5–40 MD 1 × 5–40	Hypotension, cough.
C. Calcium entry blockers			
Diltiazem	Cardizem	ID 2 × 30 DR 60–360 MD 2–3 × 30–120	Palpitations, heart block, constipation, edema.
Nifedipine	Procardia	ID 2 × 10 DR 20–180 MD 2–3 × 10–60	Headaches, flushing, hypotension, palpitations, edema.
Verapamil	Calan Isoptin	ID 2 × 80 DR 160–480 MD 2–3 × 80–160	Heart block, constipation, headaches, edema.
	Calan SR Isoptin SR	ID 1 × 120 DR 120–480 MD 1 × 120–480	

‡ID: initial dosage. DR: dosage range. MD: maintenance dosage.

brane transport systems. Regardless of their site of action along the nephron (the early distal tubule for thiazides, and the thick ascending limb of Henle's loop for "loop" diuretics), diuretics lower blood pressure because of the sodium loss which they produce. During the initiation of chronic diuretic therapy, negative sodium balance is induced, leading to a contraction of plasma and extracellular fluid volumes and a drop in cardiac output. Subsequently, blood volume returns toward normal and cardiac output rises, coincident with a fall in peripheral resistance. This "resetting" of the peripheral resistance-cardiac output relationship is unexplained but has been attributed to: (1) a decrease in vascular reactivity to pressor stimuli; (2) suppression of endogenous circulating natriuretic agents with vasoconstrictor properties; or (3) to relief of "water-logging" of the vascular wall.

As a consequence of the metabolic adjustments initiated by the natriuresis, certain biochemical abnormalities reliably follow effective thiazide or loop diuretic therapy — kaliuresis, which may cause hy-

pokalemia, and diminished uric acid clearance, which may cause hyperuricemia and gout. In addition, through mechanisms less clearly linked to natriuresis, diuretics may impair glucose tolerance and promote dyslipidemias. Combinations of thiazides and potassium-sparing agents are now widely used and seem to be largely effective in preventing hypokalemia, although such preparations are not without their own side-effects. The potassium-sparing diuretic, amiloride (Midamor®), when combined in a fixed dose with hydrochlorothiazide (Moduretic®), can cause hyponatremia, hyperuricemia and, occasionally, hypokalemia. Combinations of triamterene and hydrochlorothiazide (Dyazide®, Maxzide®) share similar problems. Neither potassium-sparing agent seems to be of benefit in reversing the changes in serum cholesterol concentration induced by thiazides, but glucose tolerance may be improved, possibly because hypokalemia may be an important link between diuretic therapy and hyperglycemia.

A drug structurally similar to both the thiazide

diuretics and the nondiuretic vasodilator, diazoxide (Hyperstat®), the indoline derivative indapamide (Lozol®) is reported to have a unique combination of both diuretic and vasodilator properties, although as noted above, this combination of effects is actually shared with other chronic diuretic therapies. Like the thiazides, the onset of the antihypertensive action of indapamide is slow (weeks to months), but indapamide may produce less hypokalemia, hyperuricemia and hypercholesterolemia than thiazides in equieffective antihypertensive doses.

Nor surprisingly, dietary sodium restriction is also capable of lowering blood pressure in patients with hypertension. Reducing sodium intake to approximately 100 mEq per day (4–6 grams of NaCl/day) lowers blood pressure significantly in approximately 50% of subjects with mild hypertension. Salt restriction also potentiates the antihypertensive effect of diuretic agents and is, in general, a useful adjunct to pharmacotherapy of hypertension.

B. SYMPATHOLYTIC AGENTS

Available agents are best subclassified according to their primary site of action, central or peripheral.

1. Centrally active agents

Centrally active sympatholytics lower blood pressure by inhibiting sympathetic outflow from the brain. Although central activity may contribute to the antihypertensive action of several drug classes, e.g., the lipid-soluble β-blocker propranolol, drugs with *primary* central activity include those that deplete catecholamines, reserpine and the related rauwolfia alkaloids, and those with adrenergic agonist properties at the α_2-receptor subtype, alphamethylnorepinephrine (derived from the prodrug alphamethyldopa [Aldomet®]), clonidine (Catapres®) and guanabenz (Wytensin®).

Reserpine, although still surprisingly widely employed, primarily in fixed-dose combinations with diuretics and/or vasodilators, e.g., Ser-Ap-Es®, can produce profound mental depression by virtue of its widespread effects on central catecholaminergic systems and is thus probably inferior to the more specific central α_2-agonists. Alphamethyldopa's (Aldomet®) central antihypertensive effect, originally attributed to the production of an inactive "false neurotransmitter" that substituted for endogenous catecholamines and decreased the effectiveness of neuronal discharge, now is known to result from the action of a primary metabolite, alphamethylnorepinephrine (produced by the sequential actions of dopa-decarboxylase and dopamine β-hydroxylase on the substrate α-methyldopa). Alphamethylnor-

epinephrine is a potent and quite specific agonist at α_2-receptors, an activity shared with the other central sympatholytics, clonidine and guanabenz. Stimulation of central α_2-receptors by any of these agents results in an inhibition of central sympathetic discharge and produces a fall in peripheral vascular resistance and blood pressure. However, at the same time, α_2 stimulation may precipitate somnolence, dry mouth and dizziness. Both the desired blood pressure lowering action and the unwanted side-effects are due to stimulation of the same receptor subtype, but there may be differences in the susceptibility to each effect that may be exploited by the use of a recently-introduced transdermal controlled-release preparation of clonidine (Catapres TTS®).

2. Peripherally Active Agents

Peripherally active sympatholytics include the neuronal blockers (guanethidine [Ismelin®], guanadrel [Hylorel®], the β-blockers, α-blockers and a combined α- and β-receptor blocker, labetalol (Normodyne®, Trandate®).

Guanethidine and guanadrel initially inhibit the release of norepinephrine from peripheral sympathetic nerves and subsequently disrupt granular storage of catecholamines, resulting in neurotransmitter depletion. Since the drugs do not penetrate the central nervous system, sedation and depression are not problems with the neuronal blockers, but, unfortunately, other disturbing effects attributable to widespread suppression of sympathetic function limit patient acceptance of these agents. Orthostatic hypotension, frequently manifested by faintness, is characteristic because guanethidine and guanadrel inhibit the reflex neurogenic cardiovascular compensations to upright posture, and gastrointestinal dysfunctions, including diarrhea and constipation, and genitourinary effects, particularly ejaculatory incompetence and renal fluid retention occur with moderate frequency.

Of the adrenergic receptor blockers, the *β-blockers* have enjoyed the most popularity as antihypertensives. Seven β-blockers are currently marketed in the U.S. (Table 1), and although there are substantial pharmacokinetic and pharmacodynamic differences, all are equally effective antihypertensives. Pharmacological differences include three clinically relevant considerations: cardioselectivity, intrinsic sympathomimetic activity (ISA) and water solubility.

Cardioselectivity refers to the relative β-blocking potency of a drug at β_1- and β_2-receptor subtypes. Since the heart is largely or exclusively populated by β_1-receptors while other sites such as bronchial and vascular smooth muscle have predominantly β_2-re-

ceptors, drugs which exhibit greater relative activity at β_1 than at β_2 sites are termed cardioselective. The rationale for the development of β_1-selective drugs was to diminish those unwanted side-effects (bronchoconstriction, peripheral vascular constriction) mediated by β_2-receptor blockade, since the antihypertensive action of the drugs seems to result from β_1-blockade. It should be recognized that cardioselectivity is only a relative selectivity; that is, given a high enough concentration of drug at either β-receptor subtype, blockade will occur. Clinically, the degree of cardioselectivity of the agents available is sufficient to offer a useful degree of differential β_1- and β_2-blockade that permits the clinician to ameliorate β_2-mediated side-effects in a substantial proportion of patients with troubling complaints of mild wheezing, cough, or cold extremities.

ISA is the pharmacologic property of partial agonist activity and in current clinical usage refers to drugs having activity at the β_1-receptor subtype. Since β_1-receptor antagonists are often structurally quite similar to β_1-receptor agonists, it has been possible to produce agents which, while competitively antagonizing the effects of endogenous circulating or neuronally released catecholamines, mildly stimulate the receptors they occupy. The net physiologic effect of these drugs thus depends on the prevailing level of β-adrenergic tone and the strength of the partial agonist potency of the drug. In states of high prevailing tone, such as congestive heart failure or dynamic exercise, β-blocking effects (cardioselective or nonselective, depending on the agent) are prominent, and heart rate and cardiac output are lowered. In states of low sympathetic tone, e.g., resting in the supine posture, administration of an agent with ISA may increase heart rate as the partial agonist property is expressed in the absence of endogenous β-adrenergic tone. In general, drugs with ISA support the basal heart rate above that seen with non-ISA β-blockers and therefore may be useful in selected patients who develop symptomatic bradycardias on non-ISA β-blockers. In addition, β-blockers with ISA seem to cause fewer disturbances in lipid metabolism than those without ISA.

The degree of lipid- or water-solubility of a compound largely dictates its route of elimination from the body and thus has a major impact on pharmacokinetics. Highly lipid-soluble agents are largely metabolized in the liver where biotransformation renders them more water-soluble and facilitates renal and biliary excretion. Since individuals may have widely different hepatic drug metabolizing capacities, plasma levels of highly lipid soluble compounds often vary greatly (20-fold) and unpredictably, necessitating dose titration to ensure adequate β-

blockade. Since the liver is a very efficient drug metabolizing system, lipid-soluble compounds are generally cleared from the circulation rapidly and consequently have short plasma half-lives. Conversely, renal excretion of drugs is relatively slow and half-lives for water-soluble compounds accordingly long. Although the antihypertensive effects of β-blockers are not strictly dependent on maintenance of β-blocking plasma concentrations, in general, the longer the plasma half-life, the longer the dosing interval. Thus, the most water-soluble agents (nadolol [Corgard®], atenolol [Tenormin®], acebutalol [Sectral®]) can be dosed once daily while highly lipid-soluble drugs (propranolol [Inderal®]) require multiple daily (2–4 times per day) dosing. Recently, a sustained-release propranolol preparation (Inderal LA®) has been introduced to allow once daily dosing of that drug.

Currently available agents permit selection of the various combinations of cardioselectivity, ISA and water solubility for particular patient needs. It should be reemphasized that such tailoring of therapy is directed solely toward avoiding side effects and increasing compliance, as all the available β-blockers have equivalent antihypertensive potency. When a β-blocker is selected as an antihypertensive to take advantage of a related activity, e.g., cardioprotection in the post-myocardial infarction patient, pharmacological differences must be considered, as not all β-blockers manifest the same activity for these non-hypertension indications.

Alpha-blocking agents such as phenoxybenzamine (Dibenzyline®) have been available for many years, but were of limited utility because they produced unacceptable physiological side-effects (tachycardia, palpitations, dizziness). These effects resulted from nonselective α-blockade at both α_1 and α_2 sites and are less prominent with the available α_1-selective agents, prazosin (Minipres®) and terazosin (Hytrin®). Selective α_1-blockade antagonizes the effect of circulating or neuronally-released catecholamines at vascular α_1-receptors without antagonizing the effect of catecholamines on α_2-receptors located on the prejunctional membranes of peripheral sympathetic nerve endings. Stimulation of these α_2-receptors decreases neurotransmitter output during subsequent nerve discharges, a form of negative feedback control. At sites innervated by sympathetic nerves, but not controlled by postjunctional α_1-receptors, such as the heart with its postjunctional β_1-receptors, normal feedback inhibition by α_2-receptor activation seems to be effective in controlling the reflex sympathetic activation resulting from the blood pressure-lowering effect of vascular α_1-blockade. Thus, prazosin causes vasodilation without prominent reflex tachycardia. The degree of blood

pressure lowering resulting from the administration of prazosin is dependent upon the level of α-adrenergic tone at the blood vessels, and particularly when such tone is high, as in the sodium-depleted state, profound hypotension may result from the first dose of prazosin. This hypotensive effect, which may be unpredictable, does not routinely occur with subsequent doses, as the cardiovascular system seems to shift to nonadrenergic mechanisms to support blood pressure.

A single agent with both α_1- and nonselective β-blocking properties, labetalol, combines the physiological profiles of the two classes. Like other α_1-blockers, labetalol lowers blood pressure acutely by vasodilation while its β-blocking properties blunt the tendency to reflex sympathetic stimulation of the heart. The net result is maintenance of cardiac output and heart rate during labelatol therapy, making the drug useful in selected patients intolerant of the negative chronotrophic and inotrophic cardiac effects of other β-blockers. In addition, labetalol has been demonstrated to be of benefit in lowering blood pressure in certain groups, such as black hypertensives, with relative resistance to the antihypertensive effects of other β-blockers. The main limitations of labetalol seem to be a fairly high incidence of side-effects, notably dizziness and gastrointestinal disturbances, the former being particularly common in diuretic-treated patients.

3. Vasodilators

Because the hemodynamic lesion of essential hypertension is increased vascular resistance, vasodilation is an attractive antihypertensive mechanism. However, as with the nonselective α-blockers, the physiologic adjustments provoked by early attempts at vasodilator monotherapy proved to be limiting. Palpitations, tachycardia, stimulation of renin and catecholamine secretion, renal salt and water retention and headaches were common side effects of monotherapy with hydralazine (Apresoline®). Vasodilators were therefore relegated to "Step 3" therapy, where they were applied in combination with diuretic and sympatholytic drugs to prevent the expression of the reflex adjustments to vasodilation. In addition to hydralazine, minoxidil (Loniten®), the most potent oral direct vasodilator available, found use as a third agent in hypertension refractory to diuretic plus sympatholytic therapy, although the unexpected provocation of hirsutism by minoxidil limited its acceptance, particularly among women. Recently, however, new vasodilator-type drugs, the angiotensin-converting-enzyme inhibitors and the calcium-entry blockers, have been gaining popularity both as monotherapies and in combination with diuretic or sympatholytic drugs.

Angiotensin converting enzyme (ACE) inhibitors competitively antagonize the carboxypeptidase enzyme responsible for the cleavage of inactive angiotensin I (itself the cleavage product of the action of renin on renin substrate) to angiotensin II. Angiotensin II is active at specific surface-membrane-bound receptor sites mediating vascular smooth muscle contraction, aldosterone secretion, thirst, and salt retention. Although the precise contribution of each action of angiotensin II to the maintenance of hypertension is unclear, blockade of angiotensin II production by ACEI effectively lowers blood pressure by reducing vascular resistance. Reflex sympathetic activation is minimal, and in most hypertensives, neither heart rate nor cardiac output is significantly affected by ACE inhibitors. Possible explanations of this blunting of the expected sympathetic response to vasodilation include increased vagal discharge and a "desensitizing" effect of ACE inhibitors at peripheral nerve endings. At present, the precise nature of the interaction of ACE inhibitors and the sympathetic nervous system is incompletely understood, but the drugs are clearly effective and well-tolerated vasodilators.

Two ACE inhibitors are currently available, captopril (Capoten®) and enalapril (Vasotec®). Both are effective inhibitors of ACE, and the drugs differ only in pharmacokinetic properties and side-effects. Captopril was the first oral ACE inhibitor released in the United States, and was initially regarded as having most promise in severe, resistant hypertensives where it was used in rather high doses (>300 mg) in patients refractory to other agents. Early reports of granulocytopenia and proteinuria associated with captopril limited physician acceptance of the agent, particularly in patients with mild-to-moderate hypertension for whom good therapeutic alternatives existed. Subsequent experience has demonstrated captopril to be generally free of serious side-effects when used at lower doses in subjects free of renal failure, which impairs captopril excretion, and collagen vascular disease, a host factor which seems to predispose patients to granulocytopenia. The observation that suppression of white cell production and the development of proteinuria seem to be similar to effects attributed to a structurally related compound, penicillamine, led to modifications of the structure of captopril to remove a free sulphydryl group at one end of the molecule. The first non-sulphydryl ACE inhibitor, enalapril, was recently introduced and has proven to be almost free of penicillamine-like side effects. It should be emphasized that many of the serious adverse effects attributed to captopril in earlier studies were probably related to the high doses of captopril employed, and such effects are rare in the lower dose range

currently recommended (Table 1). Captopril does produce several minor side-effects such as dysgeusia and rash that also may be less frequently seen with enalapril. Those side effects related to inhibition of angiotensin II production (hypotension, flushing, hyperkalemia) or to decreased bradykinin destruction (cough) are shared by both drugs.

Apart from side effects, the only notable difference between captopril and enalapril is in duration of action. Captopril has a plasma half-life of approximately two hours and is generally dosed twice daily, although recent studies suggest that some patients may be adequately controlled on once daily dosing. Enalapril is an inactive prodrug, which is converted in the liver to an active metabolite, enalaprilat. Enalaprilat has a half-life of 6–35 hours and therefore is effective when dosed once daily. Both captopril and enalaprilat are primarily renally excreted and require dosage adjustments in patients with renal insufficiency.

ACE inhibition has provoked considerable interest as an initial monotherapy for uncomplicated mild-to-moderate hypertension. The ACE inhibitors seem to be comparable in efficacy to the most widely used alternative therapies, diuretics and β-blockers, and have an apparent advantage in terms of side effects. As noted above, concerns have been raised about the metabolic side effects of diuretics and β-blockers, and ACE inhibitors do not cause hypokalemia or have significant effects on lipid metabolism. Perhaps most importantly, they do not produce central nervous system disturbances and generally are better tolerated than sympatholytic therapies. A major difficulty in justifying substitution of ACE inhibitors for diuretics or β-blockers as initial therapy is our lack of longterm efficacy experience, particularly as regards outcomes related to cardio- and cerebrovascular events.

The calcium entry blockers are a chemically diverse group of compounds that share the ability to block the influx of calcium across cell membranes. Initially developed as antiarrhythmic, antianginal agents, the three calcium entry blockers currently available, verapamil (Isoptin®, Calan®), nifedipine (Procardia®) and diltiazem (Cardizem®), all have significant and roughly equivalent antihypertensive effects. Differential sensitivity of target tissues to each drug results in differing hemodynamic profiles. Verapamil has substantial negative chronotropic and inotropic effects with relatively little vasodilating potency while nifedipine is a potent vascular smooth muscle dilator with little direct effect on cardiac tissue, and diltiazem has mixed actions at both cardiac and vascular sites. The net effect of all three drugs is to lower blood pressure. Relative tissue specificities are also important determinants of

side-effects. Verapamil can precipitate cardiac conduction system disturbances and congestive heart failure, while nifedipine may cause headaches, flushing and, via reflex activation of the sympathetic nervous system, palpitations and tachycardia sufficient to provoke angina. Diltiazem, with its more balanced actions, produces less dramatic side effects, but can slow heart rate and conduction velocity. Because calcium influx is important to the function of many noncardiovascular organs, other side effects, particularly constipation with verapamil, may be limiting in some patients. Many patients develop edema in the absence of signs or symptoms of congestive heart failure, perhaps because of a "capillary leak" induced by calcium entry blockers.

Contributing to the antihypertensive effects produced by effects of calcium entry blockers on blood vessels and the heart may be their ability to promote natriuresis while lowering blood pressure. This natriuretic property is in marked contrast to the antinatriuretic effect of most other vasodilators and may be related to either renal vasodilation or to a tubular action of calcium entry blockers. All three calcium entry blockers require two to three daily doses to achieve smooth blood pressure control. The recent introduction of sustained release preparations of verapamil (Isoptin-SR®, Calan-SR®) now permits once-daily dosing.

II. Recent Trends in Antihypertensive Therapy

The goal of antihypertensive therapy continues to be to lower the blood pressure. The rationale for this approach is the considerable evidence demonstrating reductions in fatal and nonfatal cardiovascular events when blood pressure is lowered with drugs, and it is supposed that spontaneous or nonpharmacologically induced reductions are of similar benefit. Current concerns relate less to *whether* to lower blood pressure than to *how* to lower it. Although benefits are already substantial, can we do better for our patients?

The landmark Veterans' Administration Cooperative Trial established a standardized therapeutic strategy, stepped care, for the management of all hypertensives. Stepped care is initiated with diuretic monotherapy, and in patients failing to come under adequate control, a sympatholytic drug is added, therapy progressing to a three-drug combination with the addition of a vasodilator in very resistant patients. Not only have recent drug developments (ACE inhibitors, calcium entry blockers) somewhat blurred these traditional steps, but the entire strategy is now being questioned. With the emergence of effective monotherapeutic alternatives to diuretics, nonresponders to a drug can be with-

drawn from therapy and given an agent from another class with a reasonable expectation of success. Unfortunately, specific tailoring of drug mechanism to pathophysiologic abnormality is not yet possible, but monotherapy is the norm for most mild-to-moderate hypertensives. Whether one drug is superior to another as monotherapy is currently hotly debated, although direct comparative trials are rare.

Various factors other than efficacy need to be considered in the selection of drugs for control of hypertension, the main ones being symptomatic side effects; biochemical side effects; convenience; and expense of administration. The quality of life of the patient taking medication is the most important of these. Given comparable efficacy, those antihypertensives which produce the least side effects are to be preferred. The same is true of biochemical side effects: agents which do not alter plasma lipids, serum potassium, plasma glucose or uric acid have an added advantage. Once-daily dosage and low cost are additional reasons for favoring one drug over another.

A major puzzle is the lack of evidence that drug therapy of hypertension decreases the incidence of coronary heart disease (CHD). Although epidemiologic studies amply document the fact that hypertension is a potent risk factor for CHD, most clinical trials of the value of antihypertensive drug therapy document only decreased morbidity and mortality from stroke with little or no benefit for CHD. This is a major problem, since CHD is by far the most common complication of mild hypertension, and an extremely serious one at that. Although the lack of efficacy against CHD is unexplained, and the possibility exists that positive results would have been observed if the trials had been longer or the treatment more aggressive, there is a persistent concern that beneficial effects of blood pressure reduction may have been nullified by noxious effects of drug therapy such as atherogenic dyslipidemia or hypokalemia. It should be emphasized that these concerns are purely speculative and not firmly enough grounded to warrant extrapolation to clinical practice. In fact the results of the only large, well-designed trial comparing one class of agents (diuretics) to another (β-blockers) reveal no difference in total cardiovascular complications for the two different treatments: patients treated with β-blockers had somewhat fewer CHD events, but more strokes than those treated with diuretics. The net effect, then, was the same for both pharmacologic interventions.

A prudent approach to the management of hypertension today should include a clear emphasis on nonpharmacologic therapy and the control of CHD risk factors other than elevated blood pressure. The

major considerations in pharmacologic management should be efficacy and tolerability; therefore drug therapy must be individualized: the ideal treatment is one that lowers the blood pressure while not interfering with the quality of life of the patient.

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