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# Antihypertensive Drugs
## An Overview

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## Abstract

For most patients with systemic hypertension, long-term drug treatment is indicated and is beneficial. There is overwhelming evidence to suggest that antihypertensive drugs offer protection against complications of hypertension. Whereas nondrug therapeutic options should be implemented in all patients, a vast majority will require pharmacological treatment to achieve goal blood pressure levels. Fortunately, a number of drugs are available to accomplish successful treatment of hypertensive disorders.

While it is conventional to initiate treatment with a single drug, a suitable combination of drugs is often required to control the blood pressure effectively. Although diuretics and β-blockers are effective and well tolerated, other classes of drugs are being increasingly used as the initial choice of therapy for hypertension. Every class of antihypertensive drugs offer advantages and some disadvantage; the physician should weigh the benefits and risks in selecting one drug over another. While the clinical parameters are followed in the management of patients with hypertension, it is also necessary to monitor the patients' biochemical profile periodically in order to modify and adjust the therapy accordingly. A careful selection of drug therapy along with close follow-up offers the best prospect to reduce the burden of morbidity and mortality in hypertension. This article provides an overview of drugs in the management of patients with hypertension.

Systemic hypertension is an important indication for the use of drugs in the US. Although a number of effective antihypertensive drugs are available, new agents continue to be introduced, increasing the therapeutic options for the management of patients with hypertension. While many antihypertensive drugs are equally effective in the treatment of mild to moderate (stage I - II) hypertension, specific preferences are often used in the management of hypertension reflecting the physicians' judgment and national and international guidelines. Currently available antihypertensive drugs, when complemented by lifestyle modifications, could potentially control the blood pressure in most patients.[1] Antihypertensive drugs are most effective in combination with dietary restriction of sodium and caloric intake, weight loss, increased physical fitness, and adherence to other lifestyle modifications. Despite the convincing efficacy and tolerability of antihypertensive drugs, surveys ironically indicate that only a small number of patients achieve adequate blood pressure control.[2] Most surveys indicate that blood pressure is well controlled in only about 25% of patients with hypertension. Even though the number of available drugs has increased, the number of patients with hypertension achieving the goal blood pressure has actually decreased! The reasons for poor blood pressure control are multiple, and beyond the scope of this review. Nevertheless, unsatisfactory adherence to prescribed therapy is the main reason for the alarming number of patients with uncontrolled hypertension. Whereas patients are often faulted for neglecting to take care of their hypertension, physicians should also shoulder some responsibility for not prescribing medicines in proper dosage or for using irrational combinations.

Physicians should strongly and consistently counsel the patients about the importance of antihypertensive drug therapy; drug dosages must be properly titrated to achieve the goal blood pressure levels and when necessary, combination therapy should be optimally used. Unless the patient has severe hypertension or a hypertensive emergency or urgency, blood pressure should always be reduced gradually as this avoids adverse effects and precipitous drops in blood pressure. Several classes of drugs – old and new – are widely available in the modern management of hypertension.

## 1. Diuretics

Diuretics were introduced for the treatment of hypertension nearly five decades ago; yet they remain an important current option in the treatment of hypertension. Although, their popularity as preferred antihypertensive drugs has decreased, diuretics are widely used to treat hypertension either as monotherapy or more commonly in combination with other classes of drugs. Diuretics are a gold standard against which the modern drugs such as ACE inhibitors, angiotensin receptor antagonists, or calcium channel antagonists, are often compared. Despite the ongoing debate regarding their effect on long-term outcomes, it is generally accepted that diuretics are effective antihypertensive drugs and that they offer protection against myocardial infarction, stroke and heart failure. Diuretic therapy, of course, is less expensive compared with other drugs.

Differences in their chemical structures determines the site of action and duration of activity of various diuretics.[3] Thiazide diuretics act at the distal convoluted tubule where they inhibit sodium and chloride reabsorption, thereby decreasing plasma and extracellular fluid volume and cardiac output. Although plasma volume tends to return towards normal after long-term use of diuretics, peripheral vascular resistance remains depressed. The fall in peripheral vascular resistance therefore explains the long-term antihypertensive efficacy of diuretics. A reactive increase in plasma renin activity (PRA) may blunt the antihypertensive efficacy of diuretics in some situations. ACE inhibitors potentiate the efficacy of diuretics by blocking reactive hyper-reninemia. The chemical structures of indapamide, chlorthalidone and metolazone are related to thiazides and they produce distinctive renal and cardiovascular effects.

Thiazide diuretics are as effective as other first-line therapeutic choices in the treatment of hypertension.[4] African-American patients and the elderly respond more favorably to diuretics than Caucasians and younger patients. Diuretics potentiate the antihypertensive effects of other antihypertensive drugs. Thiazide diuretics can be administered once daily or even every other day in some circumstances (table I). The initial dosage of hydrochlorothiazide can be 6.25 to 12.5 mg/day with some patients eventually requiring dosages of up to 25 to 50 mg/day. In patients with normal renal function, low dosage thiazide therapy is often effective. Thiazides become less efficacious in the presence of excessive salt intake, in patients with renal insufficiency (creatinine clearance <30 ml/min or serum creatinine >1.5 mg/dl), and in patients taking nonsteroidal inflammatory drugs. Studies indicate that long-term therapy with thiazide diuretics may protect against osteoporosis because of their hypercalcemic effect.[5]

### 1.1 Adverse Effects

Hypokalemia is a common adverse effect of thiazide diuretics; the magnitude of potassium depletion is dose dependent; low dosages producing least hypokalemia. A high salt intake[6] and other concomitant potassium-losing conditions may aggravate the problem. The degree and duration of hypokalemia govern the occurrence of potential dangers such as cardiac arrhythmias, mus-

**Table I.** Diuretics

| Drug | Therapeutic dose (mg) | Frequency of administration (times/day) |
|---|---|---|
| **Thiazides** | | |
| Chlorothiazide | 125-500 | 1 |
| Hydrochlorothiazide | 12.5-50 | 1 |
| Polythiazide | 1.0-4.0 | 1 |
| **Thiazide-related compounds** | | |
| Chlorthalidone | 12.5-50 | 1 |
| Indapamide | 1.25-2.5 | 1 |
| Metolazone | 2.5-10 | 1 |
| **Loop Diuretics** | | |
| Bumetanide | 0.5-5.0 | 1-2 |
| Ethacrynic acid | 25-100 | 1-2 |
| Furosemide | 20-480 | 2-3 |
| Torasemide | 5-40 | 1-2 |
| **Potassium-sparing agents** | | |
| Amiloride | 5-10 | 1 |
| Spironolactone | 25-100 | 1 |
| Triamterene | 50-150 | 1 |

cle weakness, polyuria, and insulin resistance.[7] Thiazide diuretics may also cause hypomagnesemia, hypercalcemia, and hyperuricemia. Long-term high dosage (>50 mg/day) thiazide therapy may cause hyperlipidemia: plasma levels of total and low density lipoprotein cholesterol may go up with no major alterations in plasma levels of high density lipoprotein cholesterol or triglycerides. Skin reactions, blood dyscrasias, acute cholecystitis, pancreatitis and vasculitis have been uncommonly reported with thiazide use; excessive volume losses can of course, cause azotemia. The relationship between thiazide use and renal cell carcinoma remains controversial.[8]

### 1.2 Special Types of Diuretics

Loop diuretics act by blocking chloride reabsorption in the thick ascending loop of Henle and thus lead to marked natriuresis. The loop diuretics are considered to be more potent than the thiazides and have a rapid onset of action. However, in uncomplicated hypertension, loop diuretics are no more effective than thiazides. Their major therapeutic role is in patients with impaired renal function (serum creatinine >1.5 mg/dl or creatinine clearance <30 ml/min), refractory edema, or congestive heart failure. Furosemide and bumetanide have to be administered at least twice daily because of their short duration of action, whereas torasemide can be given once daily. Ethacrynic acid is rarely used because of ototoxicity but can be considered in patients with sulfonamide sensitivity. The role for loop diuretics in uncomplicated hypertension is rather limited. Loop diuretics can cause electrolyte and volume depletion, and therefore should be used with appropriate precautions and under proper supervision.

## 2. Adrenergic Inhibitors

Adrenergic inhibitors have been used in the treatment of hypertension on the principle that an inappropriate level of sympathetic activity plays a pathogenetic role in hypertensive disorders. Sympathetic neurohormones such as norepinephrine and epinephrine exert a multitude of cardiovascular actions by activating the adrenergic receptors. Therefore, blockade of these receptors by pharmacological means lowers the peripheral vascular resistance or cardiac output or both, in addition to interrupting other pressor mechanisms such as the renin-angiotensin system.

### 2.1 β-Adrenoceptor Antagonists

Since their introduction in the early 1970s, β-adrenoceptor antagonists (β-blockers) have been extensively used to treat hypertension and other cardiovascular disturbances. β-Blockers have been shown to provide secondary cardioprotection after myocardial infarction which is their main therapeutic advantage.[9] A number of β-blockers are available for clinical use (table II); they are classified according to their pharmacological properties - $\beta_1$ selectivity (cardiac), lipid solubility and intrinsic sympathomimetic activity (ISA). Some drugs, such as labetalol, possess both α- and β-blocking actions. Although β-blockers lower the cardiac output acutely, their long-term action in the management of hypertension, most likely is mediated by a fall in peripheral vascular resistance. The bioavailability of lipid soluble β-blockers such as propranolol and metropolol is considerably less than that of lipophobic β-blockers such as atenolol. Both the car-

**Table II.** β-adrenoceptor antagonists

| Drug | Therapeutic dose (mg) | Frequency of administration (times/day) |
|---|---|---|
| Acebutolol | 20-1200 | 1 |
| Atenolol | 25-100 | 2 |
| Bisoprolol | 2.5-20 | 1 |
| Metoprolol | 50-200 | 1-2 |
| Nadolol | 20-240 | 1 |
| Pindolol | 10-60 | 1 |
| Propranolol | 40-240 | 2-3 |
| **Combined α- and β-blockers** | | |
| Carvedilol | 12.5-50 | 1-2 |
| Labetalol | 200-1200 | 1-2 |

dio ($\beta_1$) selective and nonselective β-blockers, however, are equally effective in the treatment of hypertension. The cardioselective β-blockers are less likely to provoke bronchospasm and peripheral vasoconstriction compared with nonselective β-blockers. It should be recognized, however, that no β-blocker is absolutely cardioselective and all β-blockers are nonselective at high dosages. It has been suggested that $\beta_1$-selective blockers tend to exert less unfavorable effects on lipid, glucose and insulin metabolism. β-Blockers such as pindolol and acebutalol cause gentle stimulation of β-receptors (ISA or partial agonistic activity) and hence are less likely to depress the cardial output or alter lipid metabolism or bronchial reactivity. Most β-blockers also demonstrate antianginal and anti-ischemic effects.[10] For cardiac protection,[11] it is best to choose a $\beta_1$-selective, non-ISA β-blocker such as metoprolol.

β-Blockers are used as monotherapy or in combination with other drugs (particularly diuretics) in the treatment of hypertension. It is generally believed that β-blockers are less effective in African-Americans[12] and in the elderly but this is not an absolute finding. While it is true that patients with high plasma renin activity respond better to β-blockers than those who have low plasma renin levels, therapy can be initiated without knowing the patients' renin status and the dosage can be adjusted as necessary. Concomitant treatment with β-blockers is also useful in patients requiring vasodilator therapy (e.g. hydralazine, minoxidil), as the latter drugs cause a reflex increase in the sympathetic activity, which can then be blunted by coadministration of a β-blocker. Patients with anxiety disorders, asymmetrical septal hypertrophy, hyperkinetic circulatory states and congestive heart failure may particularly benefit from β-blocker therapy.

### 2.2 Adverse Effects

Adverse effects from β-blockers can be largely attributed to their pharmacological effects (i.e. β-adrenoceptor blockade). Therefore, they can cause adverse events such as insomnia, depression and nightmares in some patients but not in any predictable manner. β-Blockers can negatively affect carbohydrate metabolism in several ways; the counter-regulatory responses to hypoglycemia are blunted by β-blockers with the potential danger of prolonging the degree and duration of insulin-mediated hypoglycemia. Although β-blockers can aggravate hyperglycemia in patients with diabetes mellitus, these drugs need not be avoided if there is a good indication, i.e. coronary artery disease. β-Blockers can also induce insulin resistance. Some β-blockers can raise serum triglyceride levels while lowering the serum high-density lipoprotein-cholesterol levels. β-Blockers with ISA or cardioselectivity are less likely to exert an adverse effect on lipid metabolism.[13] In susceptible individuals, β-blockers (especially, the nonselective ones) can aggravate bronchospasm. Hence considerable caution is advisable when prescribing a β-blocker to patients with asthma and/or chronic obstructive pulmonary disease. β-Blockers do not alter calcium or electrolyte metabolism significantly. β-Blockers can cause some degree of fatigue, reduce exercise performance and may aggravate vasospastic symptoms. Although abrupt discontinuation of β-blocker therapy does cause rebound hypertension, it may result in angina pectoris in patients with coronary artery disease. Whenever possible, therefore, β-blockers should be gradually tapered rather than abruptly stopped.

## 3. $\alpha_1$-Adrenoceptor Antagonists

α-Adrenoceptor antagonists ($\alpha_1$-blockers) are not widely used in the modern treatment of hypertension although their efficacy is well established. $\alpha_1$-blockers also improve insulin resistance, lipid metabolism and cause reversal of left ventricular hypertrophy (LVH). Despite these advantages, the future scope of $\alpha_1$-blockers in the treatment of hypertension is jeopardized by the findings of the antihypertensive and lipid-lowering treatment to prevent heart attack trial (ALLHAT).[14] In this major trial, the doxazosin arm was discontinued because of an increased incidence of congestive heart failure. Prazosin is a rapidly active $\alpha_1$-blocker[15] with a short duration of action, while doxazosin and terazosin have a gradual onset and sustained duration of action (table III). The antihypertensive efficacy of $\alpha_1$-blockers equals that of β-blockers, diuretics, calcium channel antagonists and ACE inhibitors. $\alpha_1$-blockers can be used as monotherapy or in combination with diuretics, calcium channel antagonists or β-blockers. The starting dosage should always be 1 mg/day and titrated up gradually to achieve the desired fall in blood pressure; long-acting $\alpha_1$-blockers such as doxazosin or terazosin can be conveniently given once daily. Although tachyphylaxis to $\alpha_1$-blockers has been reported in patients with heart failure, it does not seem to occur in patients with hypertension. Loss of blood pressure-lowering effect during $\alpha_1$-blocker therapy requires addition of a diuretic.

**Table III.** $\alpha_1$-Adrenoceptor antagonists

| Drug | Therapeutic dose (mg) | Frequency of administration (times/day) |
|---|---|---|
| Prazosin | 1-20 | 2-3 |
| Terazosin | 1-20 | 1-2 |
| Doxazosin | 1-16 | 1 |

### 3.1 Adverse Effects

Adverse effects such as headache, drowsiness and fatigue have been reported with $\alpha_1$-blockers and are probably nonspecific. First-dose hypotension mainly reported with prazosin can be avoided by giving the initial dose at bedtime and by adjusting the dosage gradually and not rapidly. This phenomenon, however, is uncommon with the second generation $\alpha_1$-blockers such as doxazosin and terazosin.

### 3.2 Other Effects Of $\alpha_1$-Blockade

$\alpha_1$-Blockers are useful in the medical management of obstructive uropathy because of benign prostatic hypertrophy. Although the relief of obstructive symptoms is most likely from an improvement in the dynamics of urine flow, $\alpha_1$-blockers may also reduce the growth of the prostate gland. At present, $\alpha_1$-blockers are perhaps more frequently used in the management of benign prostatic hyperplasia (BPH) than in hypertension. $\alpha_1$-blockers have been repeatedly shown to improve the lipid profiles and insulin resistance; these drugs enhance the activity of lipoprotein lipase and augment insulin sensitivity.[16] Despite this seemingly favorable cardiovascular profile, the doxazosin arm of ALLHAT was terminated because of increased risk of heart failure. Patients included in the ALLHAT trial were a high-risk group: with severe hypertension; diabetes mellitus; elderly; or African-Americans. One can argue that switching this high-risk population to monotherapy with an $\alpha_1$-blocker was unwise. Nevertheless, the ALLHAT[17] findings would make the choice of $\alpha_1$-blocker unattractive in preventive cardiology.

## 4. Combined $\alpha$- and $\beta$-Blockers

Labetalol and carvedilol are drugs which block both the $\beta$- and $\alpha$-adrenergic receptors; their dominant adrenergic inhibition, however, is at the $\beta$-receptor site whereas the $\alpha$-blocker component is an ancillary effect. The latter phenomenon adds to the vasodilatory actions of these compounds. Labetalol is indicated for the treatment of hypertension whereas in the US carvedilol is indicated for the treatment of mild to severe heart failure. Labetalol is also available for intravenous use to treat hypertensive emergencies and hypertensive urgencies. Because of its mechanism of action, intravenous labetalol is an attractive therapeutic option in the short-term management of severe hypertension.[18]

### 4.1 Adverse Effects

Labetalol and carvedilol can cause the same adverse effects that occur with pure $\beta$- or $\alpha$- blockers. Orthostatic hypotension can occur with large initial doses of these drugs. Labetalol has been associated with serious hepatotoxicity and therefore, periodic monitoring of liver function tests is recommended.[19]

## 5. Central $\alpha$-Adrenoceptor Agonists

The centrally acting drugs are one of the oldest classes of antihypertensive drugs and they are still used in the management of hypertension (table IV). Methyldopa, the prototypical drug in this class, was originally thought to have a peripheral action but subsequent studies suggested a central action: stimulation of $\alpha$-adrenoceptors in the vasomotor center which causes a reduction in sympathetic outflow with a resultant decrease in peripheral vascular resistance and a modest decrease in the heart rate/cardiac output. Methyldopa is still one of the most well tolerated antihypertensive agents in patients who are pregnant. The second generation $\alpha$-adrenoceptor agonists such as clonidine are more specific for the (central) imidazoline receptor and cause fewer adverse effects compared with methyldopa. Clonidine, guanabenz, guanfacine and methyldopa have similar therapeutic effects but clonidine is the most widely used drug in this class.

Clonidine can be administered orally or transdermally. Oral clonidine is given twice daily, but larger dosages should be preferably given at bedtime to reduce adverse effects; guananbenz and guanfacine can be administered once daily. The dosage of central $\alpha$-adrenoceptor agonists has to be adjusted upwards (or downwards) gradually. These drugs work best in conjunction with sodium restriction or with diuretics. Although, their use has decreased, central $\alpha$-adrenoceptor agonists (especially clonidine) are often used as a component of combination therapy in patients with difficult-to-treat hypertension. The usual therapeutic dosage of clonidine is <0.4 mg/day although the maximum dosage is 1.2 mg/day which increases the likelihood of possible adverse effects. Alternatively, clonidine can be used as a transdermal preparation; the dosage of transdermal clonidine is 0.1 to 0.3mg applied weekly.[20] The transdermal preparation may cause fewer adverse effects but some patients experience local dermal reactions. The centrally acting $\alpha$-adrenoceptor agonists can be used to produce modest bradycardia or prevent reflex tachycardia in situations where $\beta$-blockers are contraindicated. Clonidine has also been used to block withdrawal manifestations in drug ad-

**Table IV.** Central $\alpha$-adrenoceptor agonists

| Drug | Usual dosage range (mg/day) | Possible adverse effects |
|---|---|---|
| Clonidine | 0.2-1.2 | Withdrawal symptoms |
| Guanabenz | 8-32 | |
| Guanfacine | 1-3 | Withdrawal symptoms |
| Methyldopa | 500-3000 | Hepatic and 'autoimmune' disorders |

dicts. Moxonidine, which represents an improvement over clonidine , is an excellent therapeutic choice among this class of drugs; it is well tolerated and offers an important option in the management of hypertension. However, moxonidine is not available in the US.

### 5.1 Adverse Effects

The most common adverse effects of the centrally acting drugs are sedation, dry mouth, and impotence, which can be minimized by using lower dosages or with transdermal preparation of clonidine. Abrupt discontinuation of (high dosages) of clonidine may result in severe rebound hypertension.[21,22] Hemolytic anemia and hepatocellular dysfunction have been occasionally reported with methyldopa. Central α-adrenoceptor agonists may exert adverse drug interactions with tricyclic antidepressants and phenothiazines.

## 6. Peripheral Adrenergic Inhibitors

Since the sympathetic nervous system plays a role in the pathogenesis of hypertension, sympathetic blocking compounds were one of the first drugs to be developed for the treatment of hypertension (table V). In fact, before the advent of modern antihypertensive drugs, sympathetic blockers were the mainstay in the management of hypertension. However, development of other classes of antihypertensive drugs with superior tolerability profiles led to the decline in the use of sympathetic blockers. Ganglion blocking drugs, which act by interrupting the sympathetic outflow at the post-ganglionic site, are no longer available for clinical use (except for trimethaphan). Trimethaphan is still used, albeit infrequently, in the management of acute aortic dissection. Given as an intravenous drip it lowers the blood pressure, heart rate, and myocardial contractility. The fall in blood pressure, however, is not substantial unless the postural sympathetic hemodynamic reflexes are activated by raising the head end of the bed. Prolonged use of trimethaphan causes intolerable adverse effects (of ganglion blockade) such as paralytic ileus, urinary retention, and mydriasis. The place of trimethaphan in the treatment of patients with aortic dissection is uncertain because of the availability of more effective and better tolerated drugs such as labetalol and other parenteral antihypertensive agents.

Rauwolfia alkaloids, exemplified by reserpine, are hardly used in the treatment of hypertension because of unacceptable adverse effects. By causing depletion of norepinephrine stores, reserpine lowers the peripheral vascular resistance and, thereby, the blood pressure. Reserpine is an effective but poorly tolerated drug. In dosages of 0.10 to 0.50 mg/day, reserpine causes a significant fall in blood pressure[23] either as monotherapy or in combination with diuretics and/or hydralazine. Reserpine may cause nasal stuffiness, increased gastric secretions (and peptic ulceration), diarrhea, and marked depression. At the present time, there is no good reason to select reserpine over other well tolerated adrenergic inhibitors such as β-blockers, α-blockers, and central α-adrenoceptor agonists.

**Table V.** Peripheral adrenergic inhibitors

| Drug | Usual dosage range (mg/day) | Possible adverse effects |
|---|---|---|
| Guanadrel | 10-75 | Postural hypotension, diarrhea |
| Guanethidine | 10-150 | Postural hypotension, diarrhea |
| Reserpine | 0.05-0.25 | Nasal congestion, sedation, depression, activation of peptic ulcer |

Guanethidine shares similar mechanisms of action as reserpine i.e. depletion of norepinephine stores. But unlike reserpine, guanethidine has little or no effect on catecholamine stores in the brain and adrenal glands. In the 1950s and 60s, guanethindine was widely used despite several adverse effects. It has a long duration of action; the dosage is 25 to 50 mg/day. To avoid the development of 'pseudotolerance', guanethidine should be administered along with a suitable dosage of a diuretic. Adverse effects associated with the use of guanethidine include such as postural hypotension, diarrhea, retrograde ejaculation, erectile dysfunction and drug interactions with tricyclic antidepressants. Another peripheral sympathetic blocker, guanadrel, is similar to guanethidine in its action, therapeutic efficacy, and adverse effects. However, these drugs are rarely used these days because of the availability of effective and better tolerated antihypertensive agents.

## 7. ACE Inhibitors

As the name implies, ACE inhibitors decrease the formation of angiotensin II by inhibiting ACE activity. In addition, ACE inhibitors also prevent the breakdown of bradykinin, thereby potentiating its vasodilatory and other actions. Although all ACE inhibitors exert similar qualitative hemodynamic effects, there are some distinct pharmacological differences that influence their tissue affinity and metabolic fate. Chemically, ACE inhibitors are also distinguished by the presence of sulfhydryl, carboxyl or phosphoryl groups. Not only is the circulating renin-angiotensin system inhibited by ACE inhibitors but some of these drugs also block the tissue renin-angiotensin mechanisms.[24] Most ACE inhibitors are predominantly excreted by the kidney. Fosinopril is excreted both by the kidney and the liver (table VI).

ACE inhibitors relieve vasoconstriction primarily by inhibiting the formation of angiotensin II.[25] However, additional

pathways, such as potentiation of bradykinin and nitric oxide generation, are also likely to be involved in the cardiovascular and renal consequences of ACE inhibition. Angiotensin inhibition decreases aldosterone production, resulting in natriuresis and potassium retention. Plasma aldosterone levels may return to baseline values during long term therapy with ACE inhibitors. ACE inhibitors may also suppress the activity of the sympathetic nervous system, and decrease endothelin secretion. ACE inhibitors (either directly or indirectly) improve endothelial function and augment vascular distensibility. ACE inhibitors produce significant reversal of cardiac and vascular hypertrophy and protect against experimental atherosclerosis.

Whereas ACE inhibitors continue to be used widely in the treatment of hypertension, they are also beneficial in the treatment of congestive heart failure and they offer renal protection. Their hemodynamic actions, as well as their direct effects on the heart may mediate the cardiac benefits of ACE inhibitors. Renoprotection, in part, is because of the preferential dilation of the efferent arterioles which in turn reduces the intraglomerular pressure. This inhibition of glomerular hyperfiltration is thought to decrease glomerulosclerosis. ACE inhibitors are known to improve the insulin sensitivity. The renal and metabolic effects of ACE inhibitors make them a superior choice for patients with diabetes mellitus. In the Heart Outcomes Prevention and Evaluation (HOPE) study, ramipril reduced the morbidity and mortality drastically in patients who were considered to be at high risk.[26]

It is interesting to recall that ACE inhibitors were introduced to treat patients with hypertension 'unresponsive' to other agents. At the present time, ACE inhibitors are used and recommended as initial monotherapy in patients with hypertension with co-morbid conditions. At the optimal dosage, various ACE inhibitors exert similar antihypertensive effects but with variable duration of action. ACE inhibitors are generally well tolerated and the choice of one over another is dictated by the drug's duration of action and by the consideration of data related to their effects on target organs. The first ACE inhibitor, captopril, has the shortest duration of action; enalapril has an intermediate duration of action requiring twice daily administration; other ACE inhibitors have a longer duration of action permitting once daily administration. Monotherapy with ACE inhibitors is effective in 60 to 70% of patients with uncomplicated stage I-II hypertension. Caucasians, younger individuals and those with high plasma renin activity show a better response with ACE inhibitors and older patients, African-Americans[27] and those with low plasma renin activity respond less favorably to ACE inhibitors. When monotherapy is not sufficiently effective, a diuretic should be added. ACE inhibitor plus a diuretic produce substantial falls in the blood pressure.[28] In addition to this synergistic effect, ACE inhibitors minimize or even reverse the hypokalemic effects of diuretics. However, caution is advised when initiating ACE inhibitor therapy in patients already on a diuretic or who are volume depleted because of the risk of hypotension; the same precaution is valid for patients with high plasma renin activity.

ACE inhibitors provide special benefits in patients with heart failure and in those with renal dysfunction, particularly from diabetic nephropathy.[28] Studies have also shown that ACE inhibitors are cardioprotective following acute myocardial infarction. Most patients with heart failure and diabetic renal disease are candidates for ACE inhibitor therapy.

**Table VI.** ACE Inhibitors

| Drug | Therapeutic dose (mg) | Frequency of administration (times/day) |
|---|---|---|
| Benazepril | 20-40 | 1 |
| Captopril | 75-200 | 2-3 |
| Enalapril | 5-40 | 1-2 |
| Fosinopril | 10-40 | 1 |
| Lisinopril | 10-40 | 1 |
| Moexipril | 7.5-30 | 1-2 |
| Perindopril | 4-16 | 1 |
| Quinapril | 10-80 | 1 |
| Ramipril | 2.5-20 | 1 |
| Trandolapril | 1-4 | 1 |

### 7.1 Adverse Effects

The originally reported adverse effects induced by ACE inhibitors such as neutropenia or renal dysfunction are rather unusual in clinical practice because of refined patient selection and use of appropriate dosages. The relative incidence of adverse effects from various ACE inhibitors is similar at equipotent dosages. An abrupt fall in blood pressure can occur when an ACE inhibitor is given to volume depleted or patients with high plasma renin activity. The likelihood of this 'first dose' phenomenon is less likely with a low dosage or with a slow-acting ACE inhibitor. Cough (dry, hacking, nonproductive) is the most common adverse effect of ACE inhibitors; bronchospasm is uncommon. ACE inhibitor-induced cough is estimated to occur in 2 to 15% of recipients. Increased levels of bradykinin are assumed to be a causative factor in the genesis of ACE inhibitor-induced cough; a genetic polymorphism has also been suggested. ACE inhibitor-induced cough is more frequently reported (or volunteered) by certain segments of the population - women, Asians and African-Americans.[29] Angioneurotic edema, an infrequent adverse effect of ACE inhibitor therapy, is reported to occur in 0.1 to 0.2% of recipients.Taste disturbances and skin reactions have been mainly

reported with sulfhydryl-containing ACE inhibitors such as captopril. Leukopenia is more likely to occur in patients who are immunocompromised.

Serum potassium levels may rise with ACE inhibitor therapy particularly in the presence of diabetes mellitus or renal impairment. While an improvement in insulin sensitivity is a desirable effect of ACE inhibition, hypoglycemia has been rarely reported in patients with diabetes mellitus.[30] Abrupt deterioration in renal function has occurred when ACE inhibitors were given to the following subgroups of patients: severe renal damage, marked volume depletion, bilateral renal artery stenoses, stenosis of solitary kidney and severe cardiac decompensation. Hence, these drugs are to be avoided in these situations. However, a modest short term increase in serum creatinine level (up to 30%) can occur during the first several weeks of ACE inhibitor therapy in some patients[31] but the drug should not be discontinued as long-term renal protection can be expected. Pregnancy is an absolute contra-indication for ACE inhibitor therapy because of fetal (and placental) toxicity.

## 8. Angiotensin Receptor Antagonists

Orally effective angiotensin receptor antagonists represent an important therapeutic advance in the interruption of renin-angiotensin cascade to lower the blood pressure.[32] Angiotensin receptor antagonists such as saralasin were discovered more than 25 years ago but were only suitable for intravenous use. At the present time, a number of orally active angiotensin receptor antagonists are available for the treatment of hypertension[33] (table VII). Several subtypes of angiotensin II receptors have been discovered but the drugs that selectively block the $AT_1$ receptor subtype are effective in the treatment of hypertension. Angiotensin receptor antagonists block the actions of angiotensin II on the blood vessel, the heart, the adrenal cortex and possibly other tissues. Consequences of angiotensin receptor antagonism are reversal of vasoconstriction, myocardial and vascular hypertrophy and inhibition of aldosterone secretion - actions also seen with ACE inhibitors. Angiotensin receptor antagonists displace angiotensin II from its receptor sites; thus the circulating levels of angiotensin may actually rise in response to angiotensin receptor antagonists.[34] Because of angiotensin blockade, this reactive rise in plasma angiotensin II levels is not harmful. In contrast to ACE inhibitors, angiotensin receptor antagonists do not interfere with bradykinin metabolism. Since the antihypertensive effects of angiotensin receptor antagonists and ACE inhibitors are similar, it is unclear whether the lack of bradykinin potentiation with angiotensin receptor antagonists is a disadvantage.

**Table VII.** Angiotensin receptor antagonists

| Drug | Therapeutic dose (mg) | Frequency of administration (times/day) |
|---|---|---|
| Candesartan | 8-32mg | 1 |
| Eprosartan | 400-800mg | 1 |
| Irbesartan | 150-300mg | 1 |
| Losartan | 50-100mg | 1-2 |
| Telmisartan | 40-80mg | 1 |
| Valsartan | 80-320mg | 1 |

All the currently available angiotensin receptor antagonists are effective in the treatment of hypertension as monotherapy as well as in combination with diuretics. They differ in their duration of action and receptor binding characteristics. Losartan is a relatively short-acting drug and is best given twice daily. Other angiotensin receptor antagonists have a long duration of action and are effective when given once daily. Angiotensin receptor antagonists have additive antihypertensive effects when combined with a diuretic and, therefore, many angiotensin receptor antagonists are available in a fixed dose combination with hydrochlorothiazide. It is speculated that angiotensin receptor antagonists and ACE inhibitors produce additive antihypertensive effects but this aspect remains to be further studied. Like ACE inhibitors, angiotensin receptor antagonists also decrease proteinuria in patients with renal impairment.[35] However, long-term studies evaluating the renal protective and antiproteinuric studies of angiotensin receptor antagonists are currently lacking. Similarly there are no comparative data versus ACE inhibitors. It has been proposed that angiotensin receptor antagonists cause less hyperkalemia than ACE inhibitors.[36]

Like ACE inhibitors, angiotensin receptor antagonists also cause regression of LVH. On the other hand, however, effectiveness of angiotensin receptor antagonists in congestive heart failure and post myocardial infarction continues to be questioned.

### 8.1 Adverse Effects

Angiotensin receptor antagonists have an excellent adverse effect profile which is their major advantage over ACE inhibitors. Study after study has demonstrated that adverse effects with angiotensin receptor antagonists are no greater than with a placebo in patients with hypertension. Unlike ACE inhibitors, angiotensin receptor antagonists do not cause cough although surprisingly some cases of angioneurotic edema have been reported. As with ACE inhibitors, angiotensin receptor antagonists should be avoided in pregnancy. Treatment with an angiotensin receptor antagonist should be introduced cautiously in patients who are volume de-

pleted or in those with high plasma renin activity. Similarly, angiotensin receptor antagonists should be avoided in patients with bilateral renal artery stenoses or stenosis of a solitary kidney.

### 9. Calcium Channel Antagonists

Calcium channel antagonists were originally developed to treat angina pectoris or cardiac arrhythmias, but are now popular antihypertensive drugs.[37] Calcium channel antagonists have earned widespread acceptance despite occasional reports of their adverse effects.[38] From a pharmacological perspective, calcium channel antagonists are classified into dihydropyridines (e.g. amlodipine, nifedipine), benzothiazepines (diltiazem) and phenylalkylamines (verapamil).[39] Alternatively, calcium channel antagonists are also classified into (heart) rate accelerating drugs (dihydropyridines) and rate limiting drugs (verapamil, diltiazem)[40] (table VIII). The dihydropyridine calcium channel antagonists are powerful vasodilators whereas verapamil and diltiazem have moderate vasodilatory properties. Dihydropyridines promote cardiac contractility and increase AV conduction; on the other hand, verapamil and diltiazem depress myocardial contractility and slow down the AV conduction. The vasodilatory effects of calcium channel antagonists are predominantly mediated by the blockade of L-type calcium channels; binding of calcium channel antagonists to the L-type calcium channel dictates their tissue effects and duration of action.

Nifedipine capsules that lead to a rapid hemodynamic effect exemplify short-acting dihydrophridines;[41] long-acting slow release dihydropyridines are exemplified by amlodipine, felodipine, and the tablet formulation of nifedipine. Nifedipine capsules (orally or sublingually) produce a rapid fall in blood pressure and may cause tachycardia. The slow release formulations of dihydropyridines have a gradual onset but a sustained duration of action and do not activate the sympathetic nervous system to the same extent as nifedipine capsules. Dihydropyridines with a slow onset of action (amlodipine, felodipine) provide 24-hour blood pressure control with once daily administration. As the risks from short-acting calcium channel antagonists (nifedipine capsules) became evident, their use has declined significantly.

**Table VIII.** Calcium channel antagonists

| Drug | Therapeutic dose (mg) | Frequency of administration (times/day) |
|---|---|---|
| **Dihydropyridines** | | |
| Amlodipine | 2.5-10 | 1 |
| Felodipine | 2.5-10 | 1 |
| Isradipine | 2.5-10 | 1-2 |
| Nicardipine | 60-120 | 1-2 |
| Nifedipine | 30-120 | 1-2 |
| Nisoldipine | 20-140 | 1-2 |
| **Diltiazem** | 180-480 | 1-2 |
| **Verapamil** | 120-480 | 1-2 |

Calcium channel antagonists are effective as monotherapy or in combination with other antihypertensive drugs. Dihydropyridines appear to be more effective than verapamil or diltiazem in the treatment of hypertension. β-blockers can be safely combined with dihydropyridines but can produce additive bradycardia and cardiodepression when combined with verapamil or diltiazem; long-acting preparations are available for all calcium channel antagonists. Nifedipine capsules (oral/sublingual) have been used mainly to lower the blood pressure acutely, but this practice is eroding because of reports of several adverse events. Amlodipine is a popular calcium channel antagonist used widely in the treatment of hypertension.[42] It has been suggested that advancing age predisposes to greater antihypertensive response from calcium channel antagonists but this observation is likely because of the higher levels of systolic blood pressure in the elderly. African-American patients clearly respond much better to calcium channel antagonists than to ACE inhibitors or to β-blockers.[43] Dietary sodium restriction or diuretic therapy diminishes the antihypertensive effect of calcium channel antagonists whereas volume expansion and a high sodium intake may augment their efficacy; similarly salt-sensitive patients respond easily to calcium channel antagonists. It is known that calcium channel antagonists tend to exert a moderate natriuretic effect; this effect is best expressed on a high salt diet that would cause a greater fall in the blood pressure. Despite these observations, studies have shown a significantly superior effect on blood pressure when calcium channel antagonists are combined with diuretics.

The effect of calcium channel antagonists on renal function continues to be examined closely. The nondihydropyridine calcium channel antagonists may show an antiproteinuric effect but dihydropyridines do not decrease protein excretion. In the African-American Study of Kidney (AASK) disease, amlodipine (in contrast to the ACE inhibitor ramipril) did not slow the progression of renal disease. Short-acting calcium channel antagonists have been shown to increase the mortality and morbidity in patients with coronary artery disease. In contrast, long-acting calcium channel antagonists have been shown to be cardioprotective. For example in the Systolic Hypertension in Europe study, nitrendipine, a dihydropyridine calcium channel antagonist was shown to substantially reduce the risk of stroke and coronary events.[44] Slow release calcium channel antagonists have also been shown to be useful in the medical management of coronary artery disease. Verapamil and diltiazem have been shown to be cardioprotective in patients with non-Q-wave myocardial infarc-

tion. Although calcium channel antagonists have been shown to cause regression of LVH, they are not beneficial in the management of heart failure.[45] Another dihydropyridine calcium channel antagonist, nimodipine, is approved for relief of vasospasm after subarachnoid hemorrhage.[46]

### 9.1 Adverse Effects

As stated above, a short-acting calcium channel antagonists should be used with considerable caution, if at all. Nifedipine capsules can cause unwanted reduction in blood pressure and reflex tachycardia which may provoke myocardial ischemia.[47] In comparison with β-blockers, short-acting calcium channel antagonists have adverse outcomes in patients with coronary artery disease.[48] Long-acting calcium channel antagonists have a better record of tolerability.[49] Dihydropyridines can cause certain adverse effects such as headaches, flushing, and ankle edema. Verapamil can cause constipation and AV block; it should be avoided in patients with cardiac conduction disturbances, and be used with much caution in patients receiving β-blockers. Diltiazem causes similar problems, but to a lesser extent. Gingival hyperplasia has been reported with dihydropyridines. Plasma levels of calcium channel antagonists may increase when consumed with grapefruit juice.[50,51] The risks of bleeding and cancer attributed to calcium channel antagonists have not been substantiated.

## 10. Direct Vasodilators

Hypertension is characterized by increased peripheral vascular resistance, and drugs that directly relax resistance vessels would seem to be desirable in the management of high blood pressure (table IX). However, the efficacy of direct vasodilators, such as hydralazine and minoxidil, is blunted and modified by reflex responses to vasodilation. Certain important negative consequences of direct vasodilation limit the use of these drugs as monotherapy for hypertension. Direct arterial dilation triggers baroreceptor-mediated sympathetic activation,[52] resulting in tachycardia and increased cardiac output and myocardial oxygen demand, making it dangerous to use these agents alone in patients with known or suspected coronary artery disease. Second, direct vasodilators cause unpleasant adverse effects such as flushing, headache, and palpitations. Third, direct vasodilators cause significant fluid retention, which may decrease their therapeutic effectiveness. These disadvantages, however, can be overcome by combining vasodilators with antiadrenergic agents and diuretics. When used in this fashion, vasodilators are effective in the long-term treatment of hypertension, especially in patients with resistant hypertension.[53]

**Table IX.** Direct vasodilators

| Drug | Usual dosage range (mg/day) | Possible adverse effects |
|---|---|---|
| Hydralazine | 50-300 | Headaches, fluid retention, tachycardia, Lupus syndrome |
| Minoxidil | 5-100 | Hirsutism, fluid retention, tachycardia |

### 10.1 Hydralazine

Hydralazine, a typical direct arterial vasodilator, was introduced in the early 1950s for clinical use in hypertension. Although hydralazine reduces blood pressure, the problems mentioned above limited its use until β-adrenergic blockers were developed which together with diuretics prevented the adverse effects of hydralazine. Therapy with hydralazine should routinely be combined with an antiadrenergic drug and a diuretic. The predominant mode of action of hydralazine is to induce direct relaxation of vascular smooth muscle in the resistance vessels. This leads to a fall in peripheral vascular resistance. The antihypertensive effect of hydralazine is accompanied by a reflex activation of the autonomic reflexes with resultant increases in the heart rate and cardiac output. Hydralazine also stimulates the renin-angiotensin system, leading to aldosterone release, sodium retention, and expansion of plasma volume. Since the efficacy of hydralazine is best sustained in combination with a β-blocker and a diuretic, its use is restricted to patients who require multiple drug therapy. The drug can be given twice daily, despite the drugs short half-life. The total daily dosage should be limited to 200 to 300mg because higher dosages clearly pose a risk of inducing a lupus-like syndrome (see section 10.1.1). In fast acetylators, higher dosages may be used because the risk of this reaction is low. When a β-blocker is contraindicated, other antiadrenergic drugs, usually central α-adrenoceptor agonists, are appropriate alternatives.

#### *10.1.1 Adverse Effects*

Hydralazine causes numerous bothersome and sometimes serious adverse effects. In addition to the adverse effects described above, some patients develop nausea and vomiting and occasionally peripheral neuropathy. Fluid retention can cause not only edema but also 'pseudotolerance' to hydralazine, an effect that can be overcome by diuretic therapy and/or dietary salt restriction. Hydralazine-induced lupus usually presents with arthralgias and may be accompanied by malaise, weight loss, skin rash, splenomegaly, and pleural and pericardial effusions. Rarely, patients with hydralazine-induced lupus have associated glomerulonephritis. The syndrome occurs only in slow acetylators and is more

common in women. Hyrdralazine-induced lupus appears between 6 and 24 months after initiation of therapy.[54] The risk is proportional to the dosage; long-term therapy at dosages >200 mg/day clearly enhances the risk. The syndrome is reversible following discontinuation of treatment, and full recovery occurs within weeks, somewhat longer in advanced cases. In contrast to systemic lupus erythematosus, hydralazine-induced lupus is associated with antibodies directed against single-stranded DNA rather than against the native double-stranded DNA.

Therapy with hydralazine can be initiated with 10 to 25mg twice daily, which can be increased at weekly intervals to 200 to 400 mg/day. Intramuscular or intravenous administration of hydralazine is used for hypertensive crises. The dose requirements to achieve the therapeutic goal are unpredictable. The commonly used dose is 10 to 20mg, which may be repeated as necessary. Although an effect on the blood pressure may be seen in a few minutes, maximum decrease occurs between 15 and 75 minutes. Parenteral hydralazine therapy was successful and well tolerated in the management of severe hypertension in pregnancy.

### 10.2 Minoxidil

Minoxidil is a more potent vasodilator than hydralazine but is similar in its actions.[55] Although it is extremely effective, its adverse effects have limited its routine use in clinical practice, and its use is recommended only in patients with hypertension who are refractory to all other drugs. Like hydralazine, minoxidil dilates the resistance vessels directly and lowers the peripheral vascular resistances. There is some evidence that minoxidil may act by opening potassium channels at the cellular level. The dominant action of minoxidil is on the arterial side of the circulatory system. Venodilation does not occur, and so postural hypotension is not observed. As a result of marked reduction in peripheral vascular resistance, minoxidil causes considerable activation of the sympathetic nervous system and the renin-angiotensin system, with resultant reflex tachycardia and secondary hyperaldosteronism - consequences that blunt its antihypertensive actions. Minoxidil is frequently necessary in patients with marked renal insufficiency, who are often refractory to all other drugs. Minoxidil therapy is effective regardless of the severity or etiology of hypertension and the status of renal function. Unsatisfactory response to minoxidil is extremely rare in the authors clinical experience.[56,57] Prior to the availability of minoxidil, bilateral nephrectomy was the only other therapeutic option in patients with uncontrolled hypertension and renal damage. Minoxidil should always be administered with a β-blocker and a potent diuretic, usually a loop diuretic. The dosage of the β-blocker and the diuretic should be adjusted as needed to prevent tachycardia and edema formation, respectively, even if high dosages are necessary. Rarely, a loop diuretic and a thiazide or metolazone need to be used in combination to treat otherwise refractory edema. In the event of contraindications to the use of β-blockers, a centrally acting α-adrenoceptor agonist can be used.

Some studies have shown that prolonged minoxidil therapy stabilizes or improves the renal function in patients with hypertension and renal failure, and sustained blood pressure control with minoxidil occasionally has resulted in the discontinuation of dialysis. The improvement in renal function is primarily because of aggressive and effective blood pressure control, rather than a specific renoprotective effect of minoxidil.

#### *10.2.1 Adverse Effects*

In addition to fluid retention and symptoms because of the reflex activation of sympathetic tone, other specific adverse reactions occur. ST segment depression and T-wave flattening or inversion are frequently seen in patients receiving minoxidil. Whether this observation represents cardiac ischemia or is a manifestation of LVH is unclear. Pericardial effusion[58] including tamponade has also been reported in patients receiving minoxidil therapy. The true incidence of this adverse effect is not known because many patients receiving minoxidil are already predisposed to develop fluid retention as a result of cardiac or renal dysfunction. Rarely, pericarditis with effusion has been noted in some patients receiving minoxidil therapy, and clinical suspicion may warrant echocardiographic confirmation of the diagnosis and discontinuation of minoxidil therapy. Elevated pulmonary artery pressures have been documented in patients receiving long-term minoxidil therapy, an effect less likely to occur in patients receiving concurrent β-blockers. Hypertrichosis occurs in nearly all patients treated with minoxidil. This is particularly evident on the face, which is a serious limitation to the use of this drug in women. The mechanism for minoxidil-induced hair growth is not known. Hypertrichosis disappears within a few weeks after discontinuation of the drug but can also be treated with depilatory agents.

The usual starting dosage of minoxidil is 5 mg/day, and the maintenance dosage for most patients is 10 to 40 mg/day given once or twice daily in divided dosages. A few patients, particularly those with renal failure, require dosages greater than 40 to 50 mg/day to achieve a therapeutic effect.

## 11. Drug Treatment of Hypertension: A General Approach

Systemic hypertension remains a leading indication for drug therapy. While non-drug therapies are useful and often necessary, most patients require antihypertensive drugs for adequate blood

pressure control. Drug selection should be individualized based upon clinical assessment of the patient and associated morbid conditions and risk factors. Although the Joint National Committee recommends diuretics and β-blockers as initial therapy for hypertension, other classes of drugs can also be selected based upon concomitant conditions and risk factor assessment. Drug selection, therefore has to be individualized with the clinicians' judgment playing a key role in the disease management. The healthcare delivery system and formulary considerations may go against physicians' preferences with regard to drug selection. For most patients, low dose drug therapy should be instituted and uptitrated to attain the target blood pressure level. For most patients, combination therapy may be required to achieve and to maintain target blood pressure levels. Fixed-dose combination preparations have a definite place in blood pressure control. Specific drug selections should also be based upon considerations beyond blood pressure alone, e.g. presence of diabetic nephropathy, isolated systolic hypertension, etc. To assure patient compliance and participation, adverse effects and drug interactions should be minimized and avoided. The goal of antihypertensive drug therapy is to maintain target organ protection while controlling blood pressure effectively.

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