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Antihypertensive Pharmacology

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Although drug treatment of hypertension is associated with improved survival and decreased vascular complications, drug compliance is a major problem in the control of hypertension. All antihypertensive medications are associated with side effects; thus, it is a physician's responsibility to explain to each patient the side effects of the drugs he prescribes to treat hypertension, and to instill in the patient a sense of necessity for the treatment of hypertension. The choice of antihypertensive drug should be made based on each patient's lifestyle, overall health and ability to tolerate the drug. Ideally, the antihypertensive regimen should be simple, effective, convenient to take and have very few side effects.

HYPERTENSION IS A silent epidemic of the 20th century. According to the National Health Examination Survey of 1960 to 1962, 15 percent of whites and 27 percent of blacks had hypertension based on the World Health Organization criteria (blood pressure above 140/90 mm of mercury).[1] Despite availablity of adequate treatment, most hypertensive persons have inadequately controlled blood pressure. Both a lack of awareness and lack of compliance contribute to the problem.[2]

The mortality associated with hypertension and hypertension-related myocardial infarctions, cerebrovascular accidents and renal failure account for more than a million deaths per year in the United States.[3] In addition, the morbidity associated with these diseases has been estimated to cost more than $5 billion a year.[3] It is clearly less expensive to treat hypertension, both from a financial and an emotional viewpoint, than to deal with its consequences. In view of the Veterans Administration Cooperative Study, which shows that control of blood pressure does prevent some of the catastrophic consequences of prolonged hypertension,[4-6] there has been an increasing effort to educate both physicians and patients to detect and control high blood pressure.

The definition of hypertension is arbitrary because blood pressure in any population is a continuous variable. Actuarial data show that elevated blood pressure shortens life span, but what is startling is that the increased mortality begins with persons in the normotensive range.[7] Therefore, one can argue that the lower the blood pressure, the better will be the expected longevity. In the United States a blood pressure of 120/80 mm of mercury is the mean for the age group between 18 and 24 years, and this number increases with advancing age.[8] Elevation of blood pressure with advancing age is not universally seen, however, but seems to be part of our Western culture.[9] Therefore, because any definition of

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hypertension is arbitrary, it should be interpreted within each population group. Most physicians would agree that a blood pressure of 150/100 is definitely in the hypertensive range and requires some sort of treatment. With people under 40 one could argue that a blood pressure above 140/90 mm of mercury would warrant treatment, although good evidence is lacking that treatment of blood pressures in this borderline range will reduce organ damage and prolong life. Both systolic and diastolic blood pressure elevations are important in predicting morbidity and mortality from hypertension, although in most people both numbers tend to move in the same direction.[10,11] Isolated elevation of the systolic pressure is probably significant because there is retrospective evidence that elderly people with only systolic blood pressure elevation suffer increased mortality compared with normotensive controls.[12]

The physiologic basis for essential hypertension is elevated peripheral resistance. Cardiac output is usually within normal limits. Only in a small minority of hypertensive patients is increased cardiac output the cause of hypertension. This subgroup of hypertensive patients tends to be younger and has a more labile pattern of blood pressure elevations.[13-15]

The cause of most forms of hypertension is unfortunately not known. There is a likelihood that essential hypertension has multiple causes, although evidence to support this is lacking. Measurements of renin activity in hypertensive patients has received considerable attention recently, but categorizing patients by their renin levels has not improved blood pressure control and, at present, merely adds to the already skyrocketing cost of medical care.[16-21]

When a physician sees a new hypertensive patient, he or she must decide the extent of the workup necessary to exclude secondary causes of hypertension. Some 95 percent of hypertensive patients have essential hypertension and need medical therapy to control their blood pressure. By far, the majority of patients with *correctable* hypertension will have renal artery stenosis, whereas pheochromocytoma and primary hyperaldosteronism are rare. However, if the history or physical examination specifically suggests pheochromocytoma, a physician should not hesitate to measure urinary levels of catecholamines, vanillylmandelic acid, or both, because surgical operations for these patients can be lifesaving. If serum electrolytes indicate hypokalemia and alkalosis in an untreated hypertensive patient, a workup to exclude primary aldosteronism is warranted.

TABLE 1.—*Choice of Drugs in Treating Hypertension*

Diuretics
thiazides
furosemide
spironolactone
Beta-adrenergic blocking agents
propranolol
metoprolol
Central sympatholytic drugs
clonidine
methyldopa
Peripheral sympatholytic drugs
guanethidine
reserpine
prazosin
Drugs that affect vascular smooth muscle to decrease peripheral vascular resistance
hydralazine
minoxidil
diazoxide
sodium nitroprusside

The exclusion of renal artery stenosis is more difficult. The only way to absolutely exclude this disorder is by renal angiography. However, doing renal angiography on a mass scale is impractical, and intravenous pyelography will be falsely negative 30 percent of the time. Therefore, mass screening for this form of hypertension is not possible. Nevertheless, the presence of certain clinical features warrants renal arteriography. Severe hypertension in a young woman who has had no family history of hypertension should arouse a strong suspicion that fibromuscular dysplasia in one of the renal arteries may be the cause of the hypertension. A continuous abdominal bruit without any other signs of arteriosclerosis in a hypertensive person should also indicate the possibility of renal artery stenosis. Finally, anyone with normal renal function and severe hypertension that is poorly responsive to antihypertensive therapy may be a candidate for renal angiography to rule out renal artery stenosis.[22-24] In addition to the above-mentioned secondary causes of hypertension, coarctation of the aorta is a rare but easily diagnosable cause of hypertension which should never be missed if care is taken to measure blood pressure in both the upper and lower extremities.

Once a physician decides to treat a patient's hypertension medically, one of many drug regi-

mens may be chosen (see Table 1). Any drug or combination of drugs that is effective and convenient to take, and causes minimal side effects, is satisfactory.

Drugs in the Treatment of Hypertension

Diuretics

There are two types of diuretics that have been most used in the treatment of hypertension. Thiazide diuretics impair distal tubular sodium reabsorption in the kidney and loop diuretics inhibit chloride reabsorption at the ascending limb of the loop of Henle. In patients with normal renal function, both drugs lower blood pressure, but because thiazides are much cheaper and probably more effective, they have become more popular.[25-27]

The mechanism by which diuretics lower blood pressure is disputed, but the fact that they work is not. Severe sodium restriction will by itself lower the blood pressure in most hypertensive patients.[28] It is reasonable to assume that the diuretics alter salt and water balance in such a way that blood pressure is lowered. During acute diuretic therapy the blood volume and cardiac output is lowered to decrease blood pressure, but with chronic therapy the cardiac output returns to normal, peripheral resistance falls, and there is only a small but persistent reduction in extracellular water and plasma volume.[29,30] It is unlikely that thiazides have a direct vascular effect on lowering blood pressure because in neither isolated arteriolar preparations nor in anephric animals do thiazides have any vascular effect.[31]

The major side effects of diuretic therapy include hyperuricemia, hypokalemic alkalosis and hyperglycemia. Hypokalemia is usually mild and does not require specific therapy unless the patient is also taking a digitalis preparation.[32] Thiazide diuretics have been associated with elevation of serum lipids, the consequences of which are still speculative.[33] Rare allergic reactions to both thiazides and loop diuretics have been described. Reversible hearing loss has been associated with high doses of furosemide.

The aldosterone antagonist spironolactone has been used in treating hypertension. It has been postulated that spironolactone is effective in "low-renin" hypertension because the subset of patients with this condition have excess mineralocorticoid activity unrelated to aldosterone. However, hydrochlorothiazide works as well as spironolactone in hypertensive persons with low renin levels, and produces fewer side effects.[34]

For most hypertensive patients, the diuretic of choice is a thiazide. However, in patients with renal failure furosemide may be necessary to achieve a diuresis and hypotensive effect. If severe hypokalemia results from diuretic-induced secondary hyperaldosteronism, the use of spironolactone or triameterene should cause some potassium-sparing activity.

The Beta-Adrenergic Blocking Agents Propranolol and Metoprolol

Propranolol has become popular recently as an antihypertensive agent; however, its mechanism of action is not understood. Both propranolol, which blocks the β_1 (cardiac) and β_2 (vascular, bronchial) adrenergic receptors, and metoprolol, which predominately blocks the β_1 adrenergic receptors, have been shown to lower blood pressure in experimental animals and in humans.[35,36] Because selective β_2 antagonism has not been shown to lower blood pressure,[37] it appears that inhibition of the β_1 adrenergic receptor is responsible for lowering of blood pressure. Although some researchers have suggested that propranolol lowers blood pressure because it decreases plasma renin activity, there is substantial evidence against that being the only explanation.[38] Propranolol, when given chronically, lowers renin activity after the first dose, but the hypotension may not occur for as long as a week after the initiation of therapy.[39] Propranolol, when given intravenously, lowers renin activity immediately but the blood pressure does not decrease.[40] Practolol, another beta-blocking drug, has been shown to lower blood pressure without lowering basal plasma renin activity.[41]

Although other hypotheses have been put forth to explain propranolol's effect on lowering blood pressure the most consistent explanation is that it does so by decreasing cardiac output. The physiologic sequences after administration of propranolol are as follows: there is an immediate decrease in cardiac output but an increase in peripheral vascular resistance such that blood pressure does not change. The change in peripheral vascular resistance over several weeks readjusts close to baseline so that the chronic decrease in cardiac output results in arterial hypotension.[42] Because not all people respond to beta-blocking doses of propranolol in the treatment of hyperten-

sion, there is no one clearcut explanation for the mechanism by which beta-blocking agents lower blood pressure.

Propranolol by itself can be used to control blood pressure, but an additive effect has been observed when used together with a diuretic or a peripheral vasodilator, or both.[43,44]

The pharmacokinetics of propranolol are complex and have been reviewed recently.[45] Some 40 percent to 70 percent of the drug is extracted by liver before systemic availability; thus, there is a large variation among patients in the drug levels achieved after a standard dose.[46] Because measurements of its presence in the blood are not readily available, looking at decrements in tachycardia on exercise may be a reasonable way to evaluate the extent of beta blockade. The half-life of the drug is usually four to six hours, but its hypotensive effect can last much longer. It has been possible to give propranolol twice daily or even once daily without compromising blood pressure control.[47] Side effects of propranolol include heart failure, atrioventricular block, hypoglycemia, asthma, central nervous system disturbances and peripheral vascular compromise. In addition, propranolol blocks some of the warning signs and symptoms of hypoglycemia; therefore, its use may be contraindicated in insulin-dependent diabetic patients. The severe cardiac and pulmonary side effects of propranolol generally occur in patients with cardiac disease or underlying pulmonary disease and may occur even after they take a small dose. The most common complaint of patients taking propranolol is that they become easily fatigued after exertion, but usually the side effects are not incapacitating.[48] All of these side effects are the result of beta-adrenergic receptor blockade in the various tissues.

Generally, the hypotensive dosage of propranolol ranges between 160 and 640 mg a day, which may be given in two divided doses. It is important for practicing physicians to realize that the cardiac effect of propranolol is almost immediate, but the maximum hypotensive effect may take several weeks to achieve. This knowledge will avoid needless changes in drug dosages or the addition of another antihypertensive drug before a maximal response to propranolol is achieved.

Metoprolol has been released recently on the market in the United States. The drug has selective β_1 action although in very high doses it will also cause some β_2 blockade. The drug is an effective antihypertensive agent with potency comparable to propranolol. Metoprolol may be tried in hypertensive patients with asthma, but only when other drug therapy is not possible.

Central Sympatholytic Drugs

Clonidine. This is a centrally acting antihypertensive drug that was initially developed as a nasal decongestant. At present, there is a debate as to the exact mechanism of the action of clonidine, although most researchers agree that the drug's effect is related to its alpha-adrenergic agonist properties.[49] When given acutely clonidine produces alpha-adrenergically mediated vasoconstriction. However, clonidine also inhibits sympathetic outflow from the central nervous system and increases the depressor effects of baroreceptor stimulation.[50-60] This biphasic effect of the drug is best seen in an overdosed patient where the initial response is hypertension followed by a more prolonged hypotension due to inhibition of sympathetic outflow from the central nervous system.[53]

Because of the reduced sympathetic activity, clonidine lowers blood pressure by decreasing both cardiac output and peripheral resistance. The pharmacokinetics of clonidine indicate that the drug has a half-life of about 12 hours and its duration of action is also about 12 hours, although the range for both variables can span from 6 to 24 hours.[54,55] The drug is effective in lowering the blood pressure when combined with a diuretic to prevent salt and water retention.

The main problems with clonidine are the disturbing side effects to the central nervous system that include sedation and inability to concentrate. Dryness of the mouth secondary to decreased saliva flow is very common. The incidence of impotence is probably similar to that observed with other central sympatholytic drugs.[56] The drug ordinarily does not cause orthostatic hypotension, but orthostatic hypotension can occur if the patient is dehydrated.

Among the most serious side effects described for clonidine are rebound hypertension and signs of sympathetic overactivity 8 to 36 hours following sudden withdrawal of the drug. Elevated serum and urinary levels of catecholamines also have been noted in clonidine withdrawal.[57,58] Because the incidence of withdrawal is not known, a physician prescribing the drug should inform the patient about the danger of sudden cessation of therapy. If use of clonidine must be discon-

tinued, a regimen involving tapering the drug dosage over several days to a week is desirable. If rebound hypertension occurs, it can be treated by reinstituting clonidine.

The usual dosage of the drug is 0.2 mg to 1 mg a day in two divided doses. However, if the patient is experiencing withdrawal symptoms during the dosage interval, clonidine may have to be given three or four times per day. The hypotensive effect of clonidine is reversed with the use of a tricyclic antidepressant.[59] This interaction occurs probably at the central alpha-adrenergic receptor level.

Methyldopa. Methyldopa is also a centrally acting antihypertensive agent whose mechanism of action is incompletely understood. Present evidence indicates that the drug has to be metabolized to α-methylnorepinephrine in the brain to be effective.[60] In turn, α-methylnorepinephrine interacts with central alpha-adrenergic receptors to decrease sympathetic outflow.[61] Methyldopa, like clonidine, decreases blood pressure by reducing both the cardiac output and peripheral resistance.[42] The oral absorption of the drug is probably through an amino acid transport system in the small intestine. Absorption is incomplete and varies from 50 percent to 80 percent.[62,63] The plasma half-life of the drug is only one to two hours, but its hypotensive effect can last as long as 24 hours, probably because the active metabolite α-methylnorepinephine has a long half-life in the brain.[64] The drug has to be used with a diuretic to avoid salt and water retention secondary to decreased blood pressure.

As with clonidine, a major side effect involves depression of the central nervous system, including drowsiness, decreased intellectual drive and forgetfulness. Impotence and dryness of the mouth also are seen with the chronic use of methyldopa.

A positive direct Coombs test will develop in about 25 percent of persons on long-term methyldopa therapy, which in itself is harmless, except for difficulty in crossmatching blood for transfusions.[65] However, in 1 percent to 5 percent of patients with Coombs test positivity secondary to methyldopa, hemolytic anemia will develop, which will necessitate the cessation of the drug. In addition to hemolysis, the use of the drug has been associated with fever and hepatic dysfunction that can resemble either acute hepatitis or chronic active hepatitis.[66] With the removal of methyldopa there is usually complete reversal of the hepatic abnormalities, although hepatic failure has been reported.

The usual dosage of the drug is 500 mg to 2.5 grams a day in two divided doses, although the drug can be administered once per day with good blood pressure control.[67] Raising the daily dosage of methyldopa beyond 2.5 grams is not associated with an enhanced hypotensive response. The drug is a reliable antihypertensive agent with intermediate potency, but not popular with young and active hypertensive patients because of the drug's central depressant effect.

Peripheral Sympatholytic Drugs

Guanethidine. This is a potent antihypertensive agent that has been in clinical use for many years. Because of its basic guanidine group, the drug does not enter the brain and, consequently, it lacks any significant effect on the central nervous system.[68] The drug, transported into presynaptic sympathetic neurovesicles by the norepinephrine pump, depletes the norepinephrine and then inhibits its release, resulting in a functional sympathetic denervation.[69] The drug has complicated pharmacokinetics with an elimination half-life of five days. The therapeutic effect of the drug has been correlated with this terminal phase of elimination.[70,71]

Because guanethidine has to get into the adrenergic neuron to be active, any drug that interferes with the norepinephrine pump will inhibit its hypotensive effect. The tricyclic antidepressant drugs are the most potent in this respect, and can totally reverse guanethidine's hypotensive effect.[72] In addition, phenothiazines, ephedrine, amphetamines and cocaine can block uptake of guanethidine into nerve endings.[73-75]

The drug lowers blood pressure mainly by decreasing cardiac output through a reduction in venous return, an effect which is exaggerated when the patient is in an upright position. The side effects of the drug are secondary to unwanted aspects of adrenergic blockade. Postural hypotension and exercise-induced hypotension can lead to syncope. Diarrhea, retrograde ejaculation and nasal stuffiness are frequent. The drug causes salt and water retention so that concomitant use of a diuretic is necessary.[76] One of the advantages of guanethidine is that it is effective when given once a day. The daily dose varies from 10 mg to as high as 500 mg. Because the terminal half-life of guanethidine is five days, it may take as long as 20 days to reach a maximal

steady state effect. This aspect must be taken into account when the physician decides to increase the dosage of the drug. Because other drug regimens are frequently better tolerated, the use of guanethidine has decreased. However, in refractory cases of hypertension guanethidine has been used with success. Bethanidine is similar to guanethidine except that its much shorter action requires taking it more frequently. Side effects of bethanidine are similar to those produced by guanethidine.

Reserpine. Reserpine interferes with the integrity of the storage vesicles of adrenergic neurons and leads to degradation of norepinephrine by monoamine oxidase.[77] This action results in a pharmacologic adrenergic blockade. The drug readily crosses the blood-brain barrier so that its use is associated with numerous effects to the central nervous system. Reserpine is an antihypertensive drug of intermediate potency. When given orally it takes several weeks to achieve a maximal effect. The advantage of using reserpine is the convenience of once-a-day administration and its low cost. The drug has numerous side effects including sedation and disturbed thought processes. Psychotic depression has been described, especially when higher doses of the drug are used.[78] Nasal stuffiness and dryness of the mouth are common side effects. Reserpine increases gastric acid secretion and may exacerbate peptic ulcer disease. In high doses, reserpine may cause upper gastrointestinal bleeding. Reserpine's association with breast cancer has not been confirmed.[79]

The usual dosage is 0.25 mg once a day. The use of a diuretic is mandatory with reserpine to avoid salt and water retention.[80] As with guanethidine, reserpine should be reserved for patients in whom the use of other antihypertensive drugs with fewer side effects is not feasible.

Prazosin. This drug was initially marketed as a peripheral vasodilator because of its ability to inhibit phosphodiesterase, but it is also a potent postsynaptic alpha-adrenergic inhibitor. Because the in vitro concentration necessary to inhibit phosphodiesterase is almost 1,000 times that required to inhibit alpha-adrenergic receptors, it is more likely that the drug works through its adrenergic blocking properties.[81,82] Prazosin, like other alpha-adrenergic blocking agents, can cause orthostatic hypotension. This effect is especially prominent during the first few doses and seems to ameliorate with continued use of the drug.[83,84] For obscure reasons, prazosin, unlike the peripheral vasodilators, does not stimulate renin or cause reflex tachycardia in the face of lowered blood pressure.[85,86] The use of diuretics is necessary when prazosin is administered over a long time to avoid salt and water retention.

Overall, prazosin is well tolerated and has been found to be a useful antihypertensive drug of intermediate potency. The usual dosage is 2 to 20 mg per day given in two to three divided doses. The plasma half-life of the drug is 2½ to 4 hours, but the duration of effect of the drug is longer than that expected from plasma half-life.[87]

Drugs That Directly Affect Vascular Smooth Muscle

Hydralazine. Hydralazine has been on the market for over 20 years, but its popularity as an antihypertensive drug has had a recent resurgence.[88] The improved acceptance is almost entirely due to the fact that when hydralazine is combined with a beta-adrenergic blocking agent and a diuretic there is no tachyphylaxis. The drug has a direct effect on the arteriolar smooth muscle to decrease peripheral vascular resistance. However, if the drug is given alone, baroreceptor-mediated increases in cardiac output, plasma renin activity, and salt and water retention negate the hypotensive effect of the drug. Hydralazine is well absorbed from the intestine, but approximately 50 percent is metabolized during the first pass through the intestinal wall or the liver. The metabolism of hydralazine is partially under genetic control with slow acetylator phenotypes achieving higher plasma levels than fast acetylators of the drug. Although the half-life of the drug is relatively short (2 to 6 hours), the hypotensive effect can last for as long as 12 hours making administration twice a day possible.[89] The usual daily dose of hydralazine is 50 to 400 mg. The fast acetylators are the persons who may require higher doses of the drug to achieve a good antihypertensive effect.

The side effects of hydralazine are mainly related to the reflex sympathetic changes it produces. Palpitations and tremors can be reasonably controlled with beta-adrenergic receptor antagonists. The drug should not be used in patients with angina because it can preciptate myocardial infarction. The major side effect which limits hydralazine use is its ability to induce a lupus-like syndrome. This occurs more frequently in slow acetylator phenotypes and in patients receiving a

daily dose that exceeds 200 mg.[90] The lupus syndrome is reversible on withdrawal of the drug.[91] The development of drug-induced lupus carries a good prognosis because neither central nervous system symptoms nor renal abnormalities develop.

Minoxidil. Minoxidil is a drug whose mechanism of action is very similar to hydralazine except that it is more effective.[92] The drug has been released by the Food and Drug Administration (FDA) for general use as an antihypertensive agent. Experimental studies in dogs have shown right atrial hemorrhagic lesions after the use of minoxidil, but neither extensive use in humans nor in other animals has resulted in similar pathologic effects.

The drug is rapidly absorbed after oral administration, and plasma half-life is approximately four hours. The effect of the drug, however, can last as long as 24 hours, probably because the drug accumulates in vascular tissues, the site of its pharmacologic effect.[93] The drug is usually given in two divided doses, with dosage varying from 2 to 40 mg a day. As with any peripheral vasodilator, the use of minioxidil is associated with reflex tachycardia and salt and water retention[94]; thus, this drug is most effective when used with a diuretic and a beta-adrenergic blocking agent. Pulmonary hypertension has been described with the use of minoxidil, but in these cases the elevated cardiac output, fluid overload and left ventricular failure contributed more to the pulmonary hypertension than an elevated pulmonary vascular resistance due to the drug. Minoxidil when injected into the pulmonary circulation decreases pulmonary artery pressure.[95]

The major problems associated with the drug have been avid salt and water retention and unwanted hair growth. Salt and water retention can be controlled by the use of potent loop diuretics in most cases, but patients with moderate renal failure occasionally escape the effects of the diuretics. Unwanted hair growth is especially unaesthetic for women, but aside from cosmetic consequences, it has no harmful effect. Minoxidil is an extremely potent vasodilator and will lower the blood pressure in cases where other drugs have failed.[96] The use of minoxidil should be limited to patients who do not respond to conventional medications, until more widespread experience with the drug is gained.

Diazoxide. This drug is an analogue of the thiazide diuretics, but it lowers blood pressure by a different mechanism. The drug is a potent peripheral vasodilator; thus, it lowers blood pressure by reducing the peripheral resistance. Although diazoxide is more commonly given intravenously for hypertensive emergencies, the drug will lower the blood pressure when it is administered orally.

Diazoxide is well absorbed orally and has been used for many years for the treatment of idiopathic hypoglycemia. The drug is about 90 percent protein-bound. Initially, rapid bolus injection of the drug was advocated to get a good hypotensive effect, but recent evidence indicates that this is not necessary.[97,98] The fact that the drug reduces blood pressure when given orally should disclaim any theories that plasma protein-binding needs to be overcome to achieve hypotensive response. There is also evidence that the tissue-binding of diazoxide is reversible and that the hypotensive effect of the drug is proportional to the level of plasma diazoxide achieved.[99]

The drug is usually given intravenously as a 300-mg bolus injection to reduce the blood pressure acutely. This regimen is safe for most patients; however, excessive hypotension has been described with this dosage.[100] This is especially true in patients in whom there is sympathetic blockage because there is no reflex increase of cardiac output to compensate for the hypotension. Adequate hypotensive responses can be obtained by using smaller doses repeatedly until the desired effect is achieved. The drug should not be given to patients with ischemic heart disease, because the reflex tachycardia can precipitate myocardial infarction.

Diazoxide, like other vasodilators, is associated with salt and water retention; thus, a diuretic is frequently given with diazoxide. In malignant hypertension the use of diuretics with diazoxide should not be used routinely because these patients frequently suffer from volume depletion. Moderate salt restriction should be sufficient to prevent excessive accumulation of salt and water in these patients.

Hypertrichosis and hyperuricemia are seen when the drug is used chronically. Hyperglycemia can occur with only a few days' use of the drug because of its potent inhibitory effect on insulin release.[101] Blood glucose levels should be monitored closely in patients with adult-onset diabetes when diazoxide is used because the drug can precipitate hyperosmolar coma.

Nitroprusside. Sodium nitroprusside is a very potent intravenous antihypertensive agent that

has acquired popularity in the past five years. The molecular structure of the drug has a ferrous center surrounded by five cyanide groups and a nitrosyl group. It is the nitrosyl group that is responsible for the drug effect on vascular smooth muscle.[102] Unlike the other peripheral vasodilators (diazoxide, hydralazine, minoxidil), nitroprusside has a significant dilatory effect on both the venules and arterioles, thus both preload and afterload are affected. Also, unlike the other vasodilators, the use of nitroprusside is not associated with a reflex increase in cardiac output.[103] The drug is very useful for hypertensive emergencies as well as for decreasing cardiac preload and afterload in patients with congestive cardiac failure. The usual dosage is 1 μg per kg of body weight per minute, but sometimes a 20-fold to 30-fold higher dosage is required to achieve a hypotensive effect. The advantage of nitroprusside is its very rapid action which allows for fine adjustment of blood pressure by titrating the infusion rate. The disadvantage of the drug is the close nursing supervision that is required because accidental speeding up of the intravenous infusion will result in severe hypotension. The drug is unstable when exposed to light; therefore, the infusion bottle should be wrapped in aluminum foil, and a fresh solution should be prepared every four hours.

Sodium nitroprusside is metabolized initially to cyanide and then to thiocyanate.[104] Acute cyanide intoxication has been reported with the use of sodium nitroprusside, but it occurs only if the dosage of the drug is above 15 μg per kg of body weight per minute.[105,106] Prolonged therapy with the drug results in thiocyanate accumulation especially if renal function is impaired. The usual symptoms of thiocyanate toxicity are confusion, slurred speech, weakness, muscle twitching and tinnitus, and may progress to stupor if the administration of the drug is not discontinued. If prolonged infusion of sodium nitroprusside is required, thiocyanate levels should be checked at least once a day; if the level is above 10 mg per dl, the infusion needs to be terminated. Overall, sodium nitroprusside is a safe and versatile drug that has significantly improved therapy for hypertensive emergencies.

Overall Approach to Treatment of Hypertension

One of the biggest problems in the treatment of hypertension is patient compliance. It would seem logical that improving compliance would improve the overall treatment of hypertension. Because all drugs have side effects, it is important to individually tailor therapy to minimize discomfort to each patient. However, the patient must take responsibility for his illness and realize that his life-style may have to be altered slightly if he is to live longer.

One basic principle that should apply to all drug therapy is that the less frequently a drug is taken, the more likely it is that the drug will be taken. Thus, a once-a-day regimen is better than twice daily, but twice a day is better than four times a day. Because almost all antihypertensive drugs can be given twice per day, compliance from this point of view should be good. Also, the fewer the drugs used to control blood pressure, the easier will be compliance. If blood pressure could be controlled using one drug once a day, overall compliance would be expected to improve.

Another major problem in treating hypertensive patients is that most of them are asymptomatic; however, annoying side effects develop after initiation of drug therapy. Unless patients are well educated about the consequences of hypertension, it is easy to understand why many do not continue to take their medication. Implementing some self-assessment of blood pressure control has been shown to be helpful in overall compliance.[107] If a patient were to record his own blood pressure two times a day, not only would the physician get a better idea of his patient's hypertensive control, but the patient also would have some concrete goals to work towards that he could assess each day. This form of self-assessment of control would be similar to that practiced by diabetic patients who check urine glucose levels.

Recommendations for specific drugs in treating hypertension are difficult to make unless the overall life-style and habits of each patient are evaluated individually. Obviously, if a patient makes his living as a bus driver, drugs like methyldopa and clonidine will be inappropriate because of central depressive effects. A patient who is athletically active may not do well taking high doses of propranolol because of the drug's ability to inhibit exercise-induced tachycardia. However, this same patient may find low doses of propranolol combined with a peripheral vasodilator to be a satisfactory regimen. In a patient with adult-onset diabetes this condition may be

made worse by thiazide diuretics because the drugs interfere with insulin release. Yet, propranolol may be effective in such a patient. On the other hand, an insulin-dependent diabetic patient may find the use of propranolol unacceptable because it interferes with the warning signs and symptoms of hypoglycemia. Patients with stable angina pectoris may find that peripheral vasodilators such as hydralazine increase the severity of the angina, and may actually precipitate a myocardial infarction even when used together with a beta-adrenergic blocking agent.

Cost is a consideration in treating a lifelong disease. The least expensive drug for the treatment of mild hypertension is a thiazide diuretic. If the hypertension is more severe, the addition of a peripheral vasodilator and a beta-adrenergic blocker will, in most cases, bring the blood pressure under control. The advantage in using peripheral vasodilators instead of sympathetic nervous system blocking agents such as guanethidine is that there is no orthostatic component involved in lowering blood pressure. In patients with arteriosclerotic heart disease, methyldopa or clonidine can be substituted for hydralazine to avoid the risk of reflex tachycardia and increased myocardial oxygen consumption.

Conclusion

Ideally, an antihypertensive regimen should be simple (one or two drugs, twice a day) and each patient should be made aware of possible side effects of the drugs before beginning therapy. Patients should actively participate in monitoring the control of their illness. And physicians should work with patients so that together they can control blood pressure with the fewest drug side effects.

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