

Prevention of Some Complications of Essential Hypertension

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The major reason for treating hypertension is to avoid complications of the disease as it affects "target organs." Treatment of the blood pressure is not the only way to avoid these complications, but it is part of the total practice of preventive medicine. Hypertension lasts for several decades in most patients, and there is time to destroy the patient through target organ effects or to save the patient through treatment. Diabetes, atherosclerosis, and other illnesses and operations pose special hazards to the patient with hypertension. Patients take many other drugs as well, and some of them react adversely with antihypertension medicines. Complications from blood pressure drugs involve nearly every organ system, more than most physicians can remember. These may be dose-related and can often be avoided by using smaller doses of more than one drug. Certain problems occur so frequently that they should be learned well. The physician should bear in mind that whatever develops may be due to anti-hypertensive therapy. On the whole, however, medications for treatment of hypertension are remarkably safe and free from side effects.

A 35-year-old woman has a blood pressure of 200/100 mm Hg and dizziness. Her life expectancy is 77.7 years, and chances are she will need to take blood pressure medication for the rest of her life. Assuming she has essential hypertension, what complications might occur? That is the theme of this report.

Her complications are apt to arise (1) from the possible effects of hypertension on the heart, ie, failure, myocardial infarction, or angina, and/or on the kidneys or brain — namely (hemorrhage, thrombosis, or TIA); (2) from concomitant illnesses adversely affecting the blood pressure as she grows older, eg, diabetes and arteriosclerosis; (3) from operations; (4) from other drugs she may take, such as digitalis, estrogens, or alcohol; or finally (5) from the antihypertensive

medications themselves. Each type of complication will be discussed in turn with hints on how to minimize it.

More than Four Decades of Hypertension Could Destroy Her Body

The most frequent organs that are responsible for death or severe disability are the heart, brain, and kidney, but the rest of the arterial system is not immune to the devastating effects of hypertension. With every heartbeat, an increased workload is placed on the heart muscle and the need for more myocardial oxygen requires greater blood flow through the coronary arteries. Hypertension accelerates atherosclerosis throughout the vascular system. Yet, these unfortunate complications are multifactorial in origin and less apt to arise if no additional problems are added to the hypertension. Hence it is important for our patient not only to treat the hypertension but to minimize other risk factors as well.

The likelihood of heart attack probably will be diminished if the body

weight is brought to normal, if cigarette smoking stops, if an exercise program is undertaken and if, when the lipids are abnormal, a proper diet is followed. The Mr. Fit program (Multiple Risk Factor Intervention Trial) is testing the efficacy of such efforts now. It has been found feasible to prescribe such a program and it can be shown that motivated persons will adhere to it.¹ Hopefully a real drop in the incidence of new heart attacks will occur. Yet, it is remembered that a United States Public Health Service study showed that cholesterol-lowering drugs in former myocardial infarction patients proved valueless in subsequent morbidity and mortality.² A reduction in both heart attacks and strokes in the past 20 years in the United States has recently been attributed in large part to better blood pressure treatment.³ If we could help all our patients really control blood pressure and other remediable factors, what a difference it should make!

The dizziness this patient experiences may be on a cardiac basis if frequent cardiac irregularity is present — an association best tested with Holter electronic tape monitoring. However, in a typical patient with hypertension lightheadedness is less apt to be due to arrhythmia than to the high blood pressure itself. A dreaded stroke affecting the brain is a second complication which is more likely to occur in the presence of dizziness.⁴ However, blood pressure elevation in the moderate range in a young woman is not apt to signal an impending stroke. The symptom should disappear with treatment. Prevention of stroke calls for many years of effective blood pressure management as does the prevention of a heart attack. In older patients with elevated blood pressure, as with those with cerebral symptoms, the physician must be cautious in therapy so that episodes of hypotension are avoided.

The possibility of renal failure ought to be studied initially and may be a cause, as well as a result, of hypertension. As a cause of hypertension, pyelonephritis in the child is one of the most susceptible to treatment. Despite frequent recurrences, it is not necessarily a grave harbinger. Pickering⁵ has recorded 24 years of survival in two of his patients with malignant hypertension due to pyelonephritis treated with the now out-

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moded and not-too-effective kidney resection and lumbar sympathectomy. How much more fortunate our patients are now, provided they follow the treatment! In general, nephrosclerosis as a complication is managed with blood pressure control much as any other hypertension complication, except that methyldopa is especially useful, and secondly, as the clearance of creatinine drops severely to 15 ml/min, thiazides will have lost their effectiveness, and furosemide must be substituted. Moreover, use of a potassium supplement is to be avoided in renal failure, as well as triamterene and spironolactone, because of the hazard of elevated serum potassium.

Complicating Illnesses

Diabetes is the main threat, accelerating as it does the likelihood of vascular disease generally, and heart

attacks, stroke, and renal failure.⁶ The use of oral hypoglycemics and their reported excess cardiovascular mortality remains controversial. There is no evidence that these oral hypoglycemics have any effect on the blood pressure. Propranolol is the principal antihypertensive agent to avoid in the diabetic. It can erase warning symptoms that patients experience with hypoglycemia and should be used only with caution in most patients under treatment for diabetes. This is especially true in labile diabetes. The hyperglycemic effect of the thiazides is not a serious control problem and usually calls for only slight, if any, increase in oral hypoglycemics or insulin.

Medium and large vessel atherosclerosis affects most adults, but the stress of hypertension accelerates the development of these lesions. The

large vessels become less elastic, so that the "rigid pipe" phenomenon shows a wide pulse pressure with mainly systolic elevation of blood pressure. Elderly patients, particularly, have postural drop in blood pressure as they stand. The implication is that control may be more difficult, with faintness and lightheadedness common. As control of blood volume becomes more critical, the physician should approach diuretic use with more caution, avoiding dehydration. In addition, those drugs whose vascular effects rely heavily on postural blood pressure changes (methyldopa, guanethidine) are best used carefully. In general, when atherosclerosis is marked it is wise not to be hasty in lowering the blood pressure unless it is very high, nor should one use long-acting potent drugs such as guanethidine.

Table 1. Getting the Hypertensive Patient Ready for Operation

In General: Assess target organ status, especially of the heart and kidney.
Assess fluid and electrolyte balance.
Test for postural blood pressure change.
Maintain vascular volume during the operation to prevent or overcome hypotension.

Complications from specific medications and how to cope with them

Thiazides and Loop Diuretics	Stop these medications up to a week prior to major operations. Measure electrolytes, but consider giving extra potassium even if blood level is normal, especially if the patient takes digitalis. Furosemide and other diuretics may enhance effect of curare-like drugs.
Potassium-sparing drugs	Stop these along with diuretics. There is a potential problem of hyperkalemia if you "push potassium" with decreased renal function.
Methyldopa	Since catecholamine depletion may be a problem, stop drug up to a week prior to major operation, if patient's BP is near normal. Notify blood bank of possible positive Coomb's test.
Clonidine	Stop gradually up to a week before operation. Sudden withdrawal may be associated with rebound hypertension. Postoperative hypotension usually responds to isoproterenol or levarterenol.
Reserpine	Stop a week or two before operation to avoid catechol depletion, postoperative depression. Nasal congestion is a possible respiratory problem.
Hydralazine	Stop one week before major operation since most anesthetics are vasodilators, as is this drug.
Prazosin	Syncope is always a hazard from vasodilation, so stop one week before major operation.
Propranolol¹⁰	Gradually discontinue medication over one to two weeks, but cautiously in those at risk for myocardial infarction. If necessary, postoperative hypotension can be reversed by isoproterenol or levarterenol. Low doses and incomplete blockade are much less hazardous than doses in excess of 160 mg per day. Many anesthesiologists continue using propranolol throughout the operative period in selected patients.
Guanethidine	Stop one to two weeks preoperatively. This is longest acting of all antihypertensive agents. Check for postural hypotension. If catecholamine depletion is a problem, use isoproterenol or levarterenol with caution since guanethidine augments responsiveness to vasopressors and may produce arrhythmias.

Operations Pose a Different Problem

Two million patients with hypertension are anesthetized each year, so this is potentially a big problem. There is no real consensus as to the management in the perioperative period.⁷ Each case needs to be analyzed in terms of the patient's situation, the person giving the anesthesia, and the amount of blood pressure medication.

If the control has been good without much medication and the blood pressure normal in the preoperative period, it is desirable to remove all such medications in preparing the patient for operation since the pressure is apt to stay normal with bed rest in the hospital. Successful control of the blood pressure with a resetting of the pressure-regulating mechanism usually allows blood pressure to remain at a suitable level for some time.⁸ Homeostatic mechanisms in the patient will respond to operative stress better if the medication controls are removed. However, if preoperative blood pressure control has not been good or the amount of medication required has been large, the clinician must decide whether the patient will be able to withstand operation better if medications are continued throughout the procedure. Postoperative rise in blood pressure is an infrequent but often significant occurrence in patients with hypertension. This is sometimes the case in postresuscitative hypertension also. Rebound hypertension from

sudden discontinuation of medications is a threat with all short-acting blood pressure medications, but most emphasis has been given to this with clonidine.⁹ Even with that drug it is quite infrequent. In emergencies one must assess the risks and take the road most likely to lead to the fewest complications. Usually this means major reduction of the drugs in use. In general, hypotension is a greater problem in the anesthetic period than hypertension.

Gradual discontinuation of propranolol and clonidine over one to three weeks is desirable if time permits. Propranolol may increase hypotensive problems in the postoperative period since beta adrenergic blockade interferes with reflex responses which help to maintain blood pressure. Anesthetic agents clearly affect adrenergic responses and prolonged hypotension may occur postoperatively. It has been reported that there may be difficulty in restoring the heart beat in cases of arrest. A physician anesthesiologist can use appropriate anesthetic agents to minimize any adverse effects of beta blockade especially if the amount of such medication is not large. Concern over such adverse effects is not as keenly felt now as formerly. Experience with anesthetic agents and propranolol has shown generally that brief interruption of propranolol will suffice; if the daily dose has not been large (eg, 120 mg/day or less), interruption for a day or two may be all that is needed. Many patients with thyrotoxicosis are being operated upon with quite large doses of propranolol, but this requires special experience by the anesthesiologist.

Clonidine withdrawal may cause postoperative hypertension as well as withdrawal symptoms of agitation, tremors, nausea, and insomnia. Some of the latter can be avoided by intentional catecholamine depletion using reserpine during the withdrawal period, since otherwise sudden catecholamine release from rapid clonidine withdrawal is a potential hazard.

Blood volume depletion by chronic diuretic treatment makes it mandatory to assess fluid balance and electrolytes preoperatively. In most patients one may assume some potassium depletion even though the serum electrolytes are normal, and one should make compensatory adjustments. These are the most frequent of all preoperative problems

in the hypertensive patient.

If the procedure is elective and if, after discussing the relative hazards with your anesthesiologist or anesthesiologist, the clinician decides it will be safer to discontinue antihypertensive medications. Table 1 may offer some guidelines for avoiding complications.

Influence of Other Drugs as They Affect Long-Term Treatment

Digitalis usually is not a problem in hypertension if the physician is wary of the associated potassium loss from diuretics. Potassium and digitalis compete at the surface membrane, and if the potassium is deficient, digitalis effect may be more pronounced even to the point of toxicity.¹¹

Watch out for alcohol! It is often a hidden addiction in our society. Its least serious problem is excess "empty" calories making it a source of obesity. Frequently it complicates adherence. It can and does produce "dizziness" both by itself and more especially when used with a drug such as methyldopa. It can lead to auto accidents since its effect may be additive to antihypertensive drugs. The patient with an alcohol problem frequently has other problems as well —

economic, social, or emotional — and these must be treated.

Estrogens and birth control pills will often be troublesome.¹² We try to discontinue them in our patients for a period of four to six months to see if the blood pressure improves from this alone. The Surgeon General's office has warned women over 40 against chronic use of estrogens because of blood pressure increase and other reasons including danger of stroke.¹³ Blood pressure medication control often will become easier. In a prospective study in Glasgow of 186 women who took oral contraceptives for two years, systolic pressure increased in 164 ($p < 0.01$) and diastolic pressure rose in 150 cases ($p < 0.05$). The seriousness of this effect has been disputed, with a number of reports¹⁴ stating that the hazard of serious change in blood pressure occurs in only a minority of all patients. In the Glasgow study the increases were not large.

Complications of Antihypertensive Drugs

Sometimes preexisting conditions will affect your selection of drugs as you attempt to avoid complications. (See Table 2.)

Table 2. How to Avoid Complications from Preexisting Conditions

Heart Failure	Exercise caution with use of hydralazine, propranolol, guanethidine. Concentrate on diuresis.
Pregnancy	Avoid all drugs, relying more on bed rest. However, if hypertension is severe, treat as other hypertension, particularly avoiding reserpine and guanethidine. Thiazides cross placental barrier and appear in breast milk.
Hyperuricemia	Diuretics are the only hazard here. Use probenecid or allopurinol if uric acid initial level high (eg, 9 mg/dl or more). Consider prophylactic colchicine in first month with above.
Liver Disease	Generally do not use methyldopa or hydralazine. Cirrhosis can augment potassium loss with diuretics.
Renal Failure	Thiazides may be ineffective. Furosemide is effective but the physician should monitor against excessive salt loss. Methyldopa and hydralazine are useful; guanethidine should be avoided.
Depression	Reserpine and methyldopa and clonidine may accentuate depression. Tricyclic antidepressants tend to neutralize guanethidine, methyldopa, and clonidine. Lithium intoxication can result from decreased renal clearance with diuretics. Increased lithium toxicity has been reported also with methyldopa.
Lupus Erythematosus	Do not use methyldopa.
Peripheral Arteriosclerosis and Postural Hypotension	Avoid guanethidine and marked lowering of blood volume with diuretics. Propranolol and hydralazine may be useful because of less postural blood pressure fall.
Bronchial Constriction (Asthma)	Do not use propranolol or beta blockers.

How to Avoid Complications from Antihypertensive Medications

The possible effects and complications of anti-hypertensive drugs are so numerous as to require an encyclopedic mind to remember them. In general, any complication which occurs while taking medication calls for searching first for a relationship to

those drugs. Side effects of most of the drugs will be less marked if smaller amounts are used. Thus, for most patients the total daily dose of reserpine should not exceed 0.25 mg, or 400 mg of hydralazine, or 2 gm of methyldopa. Multiple drugs in smaller doses generally seem preferable to one to two drugs pushed to a maximum. (See Table 3.)

Table 3. How to Monitor Patients to Avoid Complications from Drugs

Thiazides and loop diuretics (furosemide and ethacrynic acid)	(a) Check potassium initially and at six-month intervals. Check more often if patient takes digitalis, or larger doses of diuretics, or has other conditions (postoperative state, diarrhea or use of steroids) causing potassium loss. A useful measurement is 24-hour excretion of potassium and sodium. (b) Check uric acid initially and annually. This should be done more often if there is history of gout or high initial levels. (c) Check blood sugar initially and annually. This should be done more often if there is a tendency to hyperglycemia or obesity. (d) Hypercalcemia occurs occasionally. (e) Serum PBI may decrease.
Potassium-sparing drugs (triamterine and spironolactone)	Use with caution in renal insufficiency, especially if the patient takes extra potassium. Since potassium-containing salt substitutes are available in grocery stores, caution patients to use them sparingly if taking one of these drugs. Recently the Food and Drug Administration has warned that spironolactone is tumorigenic in rodents, and that it should be limited in its use in hypertension to patients in whom other therapy is inadequate or inappropriate.
Methyldopa	(a) Check SGOT initially, after one month and annually. Check more often if there is moderate or more than moderate alcohol intake. (b) Check antinuclear antibody initially, at three to four months and annually. Check more often if there are rheumatic symptoms. (c) Check Coombs' initially, after three to four months and annually. Observe for fever (usually in first month). (d) Check blood count initially and at least semi-annually. (e) Monitor for CNS effects including depression.
Clonidine	Monitor for dry mouth, sedation, or depression. Avoid tricyclic antidepressants.
Reserpine	Monitor for depression and other CNS symptoms, bradycardia, diarrhea, nasal stuffiness. Use cautiously in patients with history of peptic ulcer, ulcerative colitis, or gallstones. There will be occasional arrhythmias when used with digitalis or quinidine.
Hydralazine	Check antinuclear antibody at outset, at three to four months and annually. Check more often if using larger doses (eg, over 200 mg/day). Monitor for headache, tachycardia, angina.
Prazosin	Monitor for syncope especially early in the course.
Propranolol	Monitor for slow heart rate and heart failure and for hypoglycemia if the patient is diabetic, and especially if he or she is labile or taking oral hypoglycemics or insulin.
Guanethidine	Watch for rise in BUN, bradycardia, diarrhea, and for congestive failure. Check for postural hypotension especially in the morning, in hot weather, or after exercise. Guanethidine is contraindicated in pheochromocytoma and concurrent use with reserpine may be unwise. Use with caution in patients with asthma, or those taking amphetamine-like compounds, stimulants (ephedrine), or tricyclic antidepressants (eg, amitriptyline). Phenothiazines and oral contraceptives may reduce the effectiveness of guanethidine.

Non-Proprietary Names and Trade-marks of Drugs

Thiazides — *Anhydron, Aquatag, Diuril, Enduron, Esidrix, Exna, Hydrodiuril, Metahydrin, Naqua, Naturetin, Oretic, Renese.*

Non-Thiazide Loop Diuretics — Furosemide, *Lasix*; Ethacrynic Acid, *Edecrin.*

Combination Diuretics — *Aldactazide, Dyazide.*

Potassium-Sparing Drugs — Spiro-nolactone, *Aldactone*; Triamterene, *Dyrenium*

Reserpine — *Raudixin, Rauwiloid, Reserpoid, Sandril, Serpasil.*

Hydralazine — *Apresoline.*

Prazosin — *Minipress.*

Propranolol — *Inderal.*

Guanethidine — *Ismelin.*

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