Approach to drug therapy for hypertension

OTTO G. KUCHEL,* MD, PH D, SC D, FRCP[C]; WILLIAM A. MAHON,† MD, MS, FRCP[C]; JOHN K. MCKENZIE,‡ MD, MRCP, FRACP, FRCP[C]; RICHARD I. OGILVIE,§ MD, FRCP[C]

Prevention of complications of hypertension requires the lowering of blood pressure. The therapeutic goal is to achieve and maintain a diastolic pressure of less than 90 mm Hg with minimal adverse effects. The treatment of patients with established diastolic blood pressures between 90 and 104 mm Hg (determined from three separate readings) should be individualized; general measures such as weight loss and salt restriction should be tried first as an alternative to drug therapy. Patients with diastolic pressure in excess of 104 mm Hg should be treated with antihypertensive drugs; the first step should be the use of a thiazide diuretic in addition to general measures. Patients with diastolic pressures of 90 to 115 mm Hg may require the addition of a β-adrenergic-receptor antagonist, methyldopa or clonidine if the therapeutic goal is not achieved; rarely they require the further addition of hydralazine or prazosin. Patients with diastolic pressures of 116 to 129 mm Hg usually require initially both a thiazide diuretic and a β-blocker, methyldopa or clonidine; if the therapeutic goal is not achieved, hydralazine or prazosin is added, and if a further hypotensive effect is required guanethidine can be added. Patients with severe hypertension (diastolic pressures greater than 130 mm Hg) may require urgent treatment with combinations of drugs of all three levels. Emphasis should be placed on individualized therapy and patient compliance in the assessment of therapeutic failures.

These "step-care" guidelines represent a framework for antihypertensive therapy devised from information available in 1977. It is not a rigid scheme and should be adjusted to the individual patient to ensure as normal a life as possible.

Il est essentiel de traiter l'hypertension pour en prévenir les complications majeures. La thérapie a pour but d'atteindre et de maintenir une pression diastolique inférieure à 90 mm Hg avec le minimum d'effets nocifs. On doit personnaliser le traitement chez les patients dont la tension diastolique (après au moins trois lectures) se situe entre 90 et 104 mm Hg. Avant de recourir aux médicaments, il est important d'essayer d'abord des moyens d'ordre plus général, comme perdre du poids et diminuer la consommation de sel. Les patients dont la pression diastolique excède 104 mm Hg devraient être traités avec des médicaments antihypertensifs comme un diurétique thiazide, en plus des moyens généraux. Les patients dont la pression se situe entre 90 et 115 mm Hg pourraient requérir en plus un agent bloqueur des récepteurs β-adrénergiques, méthyldopa ou clonidine; on devra parfois ajouter de l'hydralazine ou de la prazosine. Les patients dont la tension diastolique se situe entre 116 et 129 mm Hg exigent ordinairement un diurétique thiazide et un β-bloqueur, méthyldopa ou clonidine; en cas d'échec on devra ajouter de l'hydralazine ou de la prazosine. Dans les cas où ces médicaments s'avéreraient insuffisants, on ajoutera un dérivé de la guanidine. Il est possible que les patients souffrant d'hypertension sévère (dont la pression diastolique se situe au-delà de 130 mm Hg) requièrent un traitement d'urgence basé sur une association des médicaments des trois phases. On insistera sur le caractère individuel de la thérapie et sur la nécessité pour le patient de reconnaître ses manques de fidélité au traitement.

Ces directives constituent un cadre pour le traitement de l'hypertension; elles ont été établies à partir de l'information disponible en 1977. Elles doivent être adaptées à chaque patient en vue de lui assurer un mode de vie aussi normal que possible.

Elevated blood pressure is found in approximately 10% of the population. It should be considered a major risk factor for stroke, congestive heart failure, renal insufficiency and ischemic heart disease. Prevention of these problems requires detection and treatment of hypertension.

It has been demonstrated that treatment benefit occurs in men whose diastolic blood pressure during placebo therapy is consistently greater than 104 mm Hg. Patients whose diastolic blood pressure is repeatedly in excess of 104 mm Hg should be treated. There is no comparable evidence that patients whose diastolic blood pressure is consistently between 90 and 104 mm Hg should be treated, although it is considered that this

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*Professor of medicine, University of Montreal and Hôtel-Dieu Hospital, and director, laboratory of the autonomic nervous system, Clinical Research Institute of Montreal

†Staff member, Toronto General Hospital, and associate professor of medicine and pharmacology, University of Toronto

‡Staff member, Health Sciences Centre, and associate professor of internal medicine and pharmacology, University of Manitoba, Winnipeg

§Director, clinical pharmacology division, department of medicine, Montreal General Hospital, and professor and chairman, department of pharmacology and therapeutics, McGill University, Montreal

Reprint requests to: Dr. Otto G. Kuchel, Institut de recherches cliniques de Montréal, 110 ave des Pins ouest, Montréal, PQ H2W 1R7

group should receive treatment if other complications or risk factors, such as left ventricular hypertrophy, hyperlipidemia, diabetes mellitus, obesity, being male or smoking, exist. There is no agreement that patients with or without these risk factors whose diastolic pressure is occasionally above 90 mm Hg should be treated.

Increased systolic blood pressure is recognized as a significant risk factor; however, the benefits of decreasing the systolic pressure are unknown. The treatment guidelines presented in this paper are based only on levels of diastolic blood pressure because taking into account both diastolic and systolic blood pressure levels would make the guidelines unduly complex. The therapy proposed will usually reduce both the systolic and the diastolic blood pressure.

Blood pressure assessment should include casual readings on at least three separate occasions, preferably with some readings taken after the subject has been resting recumbent for 15 minutes.

Goals of therapy

The first goal is to achieve and maintain a diastolic blood pressure of less than 90 mm Hg with minimal adverse effects. To achieve this goal for patients with diastolic pressures in excess of 104 mm Hg antihypertensive drug therapy is required in addition to the general measures listed below.

For patients whose diastolic pressure lies between 90 and 104 mm Hg treatment should be individualized. Reduction of excessive salt intake, weight loss or discontinuation of oral contraceptive therapy may lower the blood pressure, but if this is not effective after 3 to 6 months specific drug therapy may be necessary. Individuals with a diastolic pressure in this range who are not given drug therapy should be examined at intervals of 3 months.

The step-care approach

The therapeutic regimen proposed below uses the "step-care" approach of drug administration. This program calls for initiating therapy with small doses of an antihypertensive drug, increasing the dose to the maximum recommended for the drug and then, if necessary, adding other drugs sequentially as needed. The dose of each additional drug is small initially and increased as required. An important feature of such a plan includes regular re-evaluation of the blood pressure and adjustment of the treatment regimen by increasing or decreasing the dose of each drug as needed.

A variety of effective therapeutic programs exists. If two different drug regimens lower the blood pressure equally, there is little reason to suppose that one is preferable to the other unless it minimizes adverse effects, patient's inconvenience, frequency of drug administration or cost.

Tranquillizers and sedatives are usually not effective in lowering the blood pressure and should not be used as primary therapeutic agents.

No single drug or combination of drugs will be effective in all patients, and alternative therapy should be considered for some individuals.

Therapy should not be started with combination products having fixed doses. It is always better to adjust the dose of each antihypertensive drug separately. When two or more drugs are needed and the optimum maintenance doses correspond to the doses of a combination product,

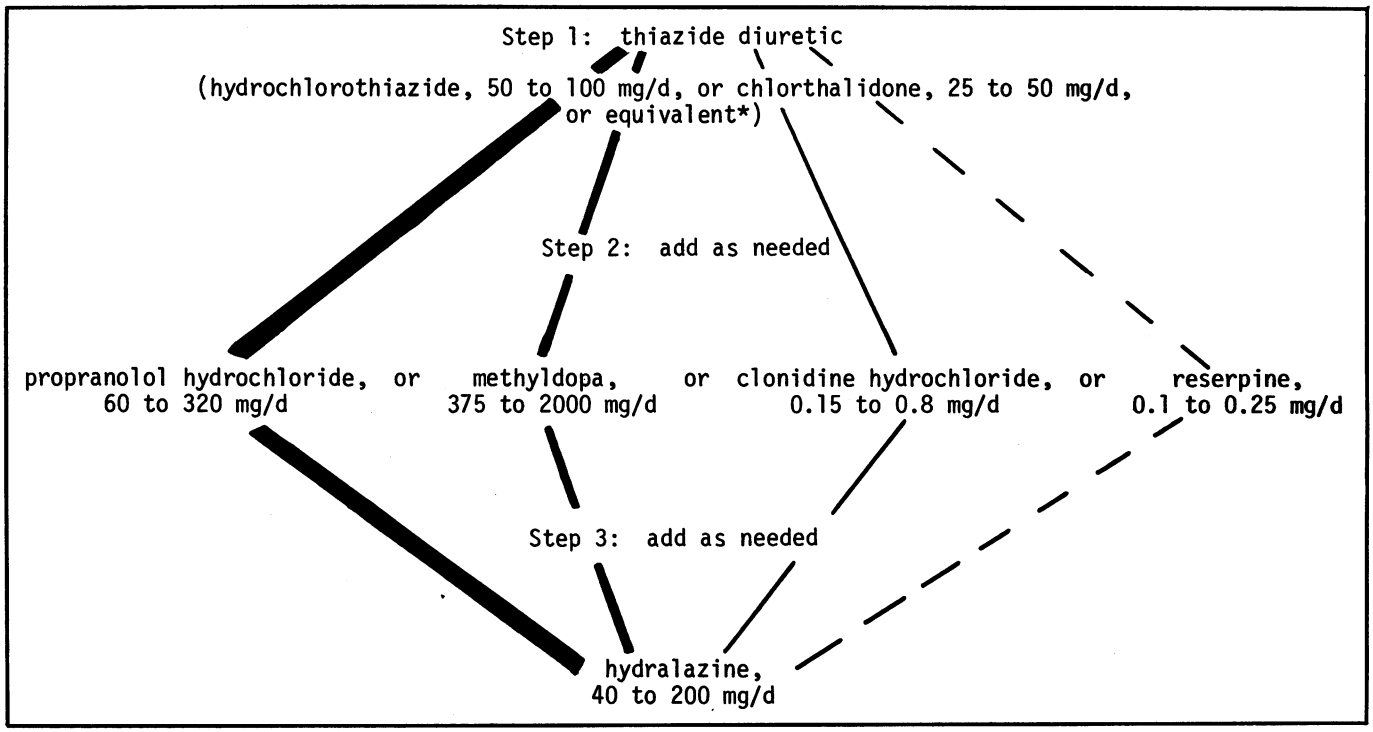

FIG. 1—Suggested regimen for management of mild to moderate hypertension (diastolic blood pressure between 90 and 115 mm Hg). Thickness of lines indicates authors' treatment preference. *See Table I. Alternative to propranolol: metoprolol tartrate, 150 to 800 mg/d. Alternative to hydralazine: prazosin hydrochloride, 0.5 to 20 mg/d.

there is no harm in using the combination drug. For further adjustment of doses, however, it is best to use the individual drugs again.

Figs. 1 and 2 display the drugs that are frequently used and found satisfactory in Canada. The regimens recommended in the figures follow the step-care program. The doses given represent the range usually found effective, the upper value being the maximum daily dose recommended.

For selection of the therapeutic regimen, patients can be divided into three groups according to the average diastolic blood pressure:

- Group 1: Patients with an established diastolic pressure between 90 and 115 mm Hg (mild to moderate hypertension), for whom the regimen in Fig. 1 is suggested.
- Group 2: Patients with an established diastolic pressure between 116 and 129 mm Hg (moderately severe hypertension), for whom the regimen in Fig. 2 is suggested.
- Group 3: Patients with an established diastolic pressure of 130 mm Hg or greater (severe hypertension), for whom the regimen in Fig. 2 is suggested.

Management of mild to moderate hypertension

Step 1

The first step in the recommended program should ordinarily be administration of a thiazide-type diuretic such as hydrochlorothiazide or chlorthalidone. Antihypertensive effects of these drugs have a definite ceiling. Higher doses rarely give additional benefits and they cause more marked biochemical abnormalities.

Apart from hydrochlorothiazide and chlorthalidone, a large number of thiazide-type diuretics are marketed in Canada, any one of which may be used as an alternative. There is little difference in the effects of the thiazide-type diuretics, although daily dose and duration of action vary (Table I).

- *Mode of action:* Uncertain. An effect on vascular smooth muscle, perhaps mediated through a reduction in intracellular concentrations of sodium and water, has been suggested.
- *Dose schedule:* Once per day.
- *Average hypotensive effect:* Decrease of 10% to 15% in mean arterial pressure.*
- *Interval between each change of dose:* Four to 8 weeks.
- *Advantages:* Effective alone in approximately 50% of patients; relatively low toxicity; cheap.
- *Adverse effects limiting clinical use:* Metabolic (hypokalemia, hyperglycemia and hyperuricemia) and hemodynamic (tachycardia, postural hypotension and prerenal azotemia due to excessive diuresis).

Hypokalemia occurs commonly in patients during long-term therapy with a thiazide-type diuretic. Combined treatment with a diuretic and a digitalis preparation requires particular attention because hypokalemia increases the toxicity of digitalis. Dietary potassium supplements are usually sufficient to prevent reduction of potassium stores. Asymptomatic hypokalemia (serum potassium concentration 3.1 to 3.5 mmol/L in blood taken without a tourniquet) usually need not be treated. When symptoms of hypokalemia develop, the serum potassium concentration is 3.0 mmol/L or less, or the patient is receiving a digitalis preparation, a potassium supplement or a potas-

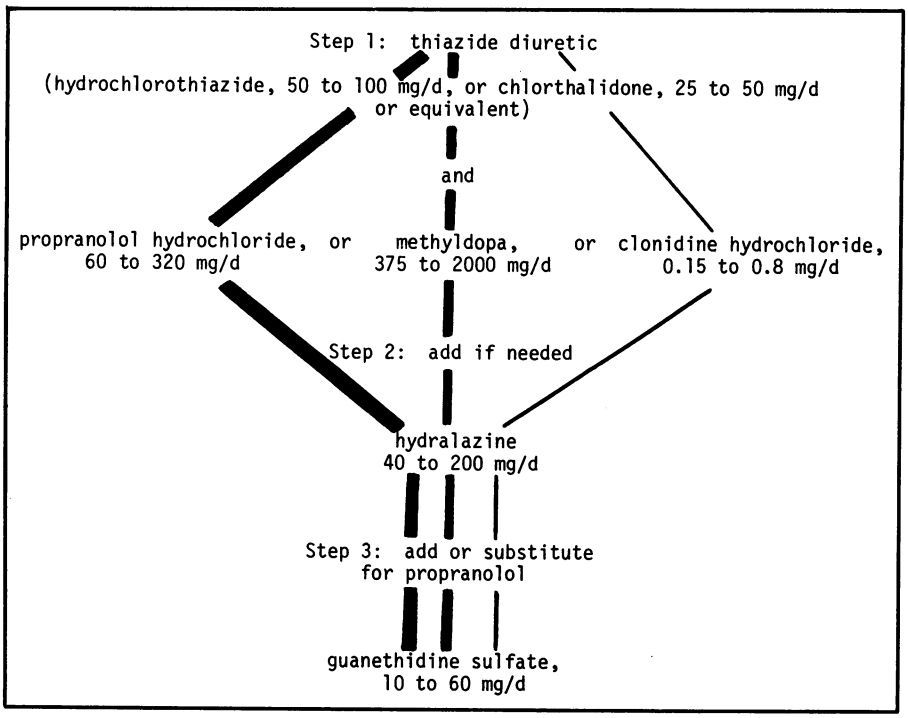

FIG. 2—Suggested regimen for management of moderate to severe hypertension (diastolic blood pressure 116 mg Hg or greater). Interpretation of line thickness and alternatives as in Fig. 1. Alternative to guanethidine: bethanidine sulfate, 15 to 150 mg/d, or debrisoquine sulfate, 15 to 60 mg/d.

*Mean arterial pressure = diastolic pressure + 1/3 (systolic pressure — diastolic pressure). For example, with a blood pressure of 160/100 mm Hg the mean arterial pressure = 100 + 1/3 (160 — 100) = 120.

Table I—Available thiazide-type diuretics

Diuretic	Dose range (mg/d)	Range of duration of action (h)
Sulfonamide derivatives		
Thiazides and thiazide derivatives		
Benzthiazide	50–200	12–18
Benzydroflumethiazide	5–20	18–24
Chlorothiazide	500–1000	6–12
Chlorthalidone	25–100	24–48
Hydrochlorothiazide	50–100	6–12
Hydroflumethiazide	50–100	12–24
Methychlothiazide	2.5–5	24
Metolazone	2.5–10	12–24
Polythiazide	2–4	24–36
Quinethazone	50–100	18–24
Trichlormethiazide	2–4	24
Nonthiazide agent		
Furosemide	80–320	4–6
Potassium-sparing agents		
Spironolactone	50–100	2–8
Triamterene	50–300	2–8

sium-sparing diuretic (spironolactone or triamterene) should be given in addition to a thiazide-type diuretic. If a potassium supplement is prescribed, a palatable liquid form of potassium chloride is preferable; enteric-coated preparations should be avoided. Potassium supplements should never be used with potassium-sparing diuretics. In patients with normokalemia, caution should be exercised in the use of potassium supplements and potassium-sparing diuretics, and both should be avoided in patients with any degree of renal insufficiency.

Potassium-sparing diuretics: Spironolactone, an aldosterone antagonist, has an antihypertensive effect. In contrast, triamterene has not been shown to have appreciable antihypertensive activity.

● *Adverse effects limiting clinical use:* Both drugs can cause hyperkalemia, especially in patients with impaired renal function and gastrointestinal upset. Spironolactone can also cause gynecomastia, impotence and menstrual irregularities. The drug has been shown to induce tumours in rats, but the clinical significance of this finding is not clear.

In certain instances other diuretics may be substituted for thiazide-type agents. Spironolactone may be given to patients with diabetes mellitus who have poorly controlled hyperglycemia. Some practitioners avoid thiazide-type diuretics entirely in hypertensive diabetic patients. Spironolactone may be substituted for a thiazide-type diuretic in patients with symptomatic gout, otherwise allopurinol can be used to control hyperuricemia induced by thiazide-type diuretics and the thiazide treatment continued. In instances of allergy to thiazides, other diuretics such as spironolactone or possibly furosemide may be tried. Furosemide may be useful in promoting sodium and water loss in patients with renal insufficiency (serum creatinine concentration greater than 180 μmol/L [2 mg/dL]; creatinine clearance less than 30 mL/min). Additional antihypertensive drugs are usually required to control the blood pressure in these patients.

Step 2

The therapeutic goal may not be achieved with the maximum recommended dose of a diuretic. As a general rule, the diuretic should be continued and another antihypertensive agent added to the therapeutic regimen.

There are several alternative step 2 drugs, all of which act on the sympathetic nervous system. The choice depends more on the associated adverse effects than on comparative efficacy. Whichever drug is chosen, it should be administered in small doses and the dose increased gradually until the therapeutic effect has been achieved, the maximum recommended dose has been given or unacceptable adverse effects have occurred.

Beta-adrenergic-receptor antagonists (β-blockers):

● *Mode of action:* Uncertain. Beta-adrenergic blockade with some specific action on central blood pressure control is suggested.

● *Dose schedule:* Two to four times per day.

● *Average hypotensive effect:* Decrease of 10% to 20% in mean arterial pressure.

● *Interval between each change of dose:* Two to 4 weeks.

● *Advantages*: Infrequent orthostatic and exercise hypotension.

● *Adverse effects limiting clinical use:*

— Bronchoconstriction: Nonselective β-blockers (e.g., propranolol) are contraindicated in patients with bronchoconstriction. Some practitioners suggest that cardioselective β-blockers (e.g., metoprolol) may be carefully tried in conjunction with bronchodilators in patients with mild bronchoconstriction.

— Reduction of cardiac output, which may lead to cardiac failure: Beta-blockers are contraindicated in patients with congestive heart failure and should be used with great caution in patients with diminished cardiac reserves.

— Bradycardia: Beta-blockers are contraindicated in patients with profound sinus bradycardia or heart block greater than second degree.

— Peripheral vascular insufficiency: Symptoms of peripheral vascular insufficiency or Raynaud's disease may be aggravated by β-blocker therapy.

— Hypoglycemia: Beta-blockers should be used with great care in patients with diabetes mellitus.

— Central nervous system effects: Insomnia, depression, hallucinations, nightmares and anxiety.

— Miscellaneous: Gastrointestinal tract disturbances, including nausea and vomiting; allergic reactions; rarely leukopenia; and thrombocytopenia.

In patients with coronary artery disease, discontinuation of β-blocker therapy should be done gradually over 2 weeks because sudden withdrawal may be associated with exacerbation of angina, or myocardial infarction.

Methyldopa:

● *Mode of action:* Inhibition of the medullary vasomotor centre.

● *Dose schedule:* Two to four times per day.

● *Average hypotensive effect:* Decrease of 15% to 20% in mean arterial pressure.

● *Interval between each change of dose:* Two to 4 weeks.

● *Advantages:* Does not depress cardiac function or increase the cardiac rate.

● *Adverse effects limiting clinical use:* Drowsiness, sedation, orthostatic hypotension, sexual dysfunction, hemolytic anemia, hepatitis, dry mouth, gastrointestinal tract disturbances, drug fever, rashes and weight gain. This drug should not be used in patients with liver disease.

Clonidine hydrochloride:

● *Mode of action:* Inhibition of the medullary vasomotor centre.

● *Dose schedule:* Three to four times per day.

● *Average hypotensive effect:* Decrease of 15% to 20% in mean arterial pressure.

● *Interval between each change of dose:* Two to 4 weeks.

● *Advantages:* Does not depress cardiac function or increase the cardiac rate.

● *Adverse effects limiting clinical use:* Sedation, somnolence, dry mouth, headache, tremor, gastrointestinal tract disturbances including constipation, and impotence. Severe "rebound" hypertension, with headache, anxiety and hyperirritability, may occur after sudden discontinuation of the drug. Patient's compliance is very important.

Reserpine: In doses unlikely to cause adverse reactions, this drug is usually less effective than the drugs already discussed.

● *Mode of action:* Central and peripheral interference with chemical neurotransmission.

● *Dose schedule:* Once per day.

● *Average hypotensive effect:* Decrease of 10% to 15% in mean arterial pressure.

● *Interval between each change of dose:* Four to 8 weeks.

● *Advantages:* Cheaper than other step 2 drugs.

● *Adverse effects limiting clinical use:* Depression (use of this drug is therefore contraindicated in patients with past or present depression), drowsiness, lethargy, bizarre dreams, confusion, parkinsonian state; parasympathetic dominance leading to nasal congestion, stuffiness, salivation, gastrointestinal tract hypermotility and increased gastric acid secretion, which may initiate peptic ulceration (this drug should therefore not be used in patients with a history of peptic ulcer or ulcerative colitis); weight gain; and impotence.

Step 3

When a third step is needed, a peripheral vasodilator such as hydralazine or prazosin may be added to the regimen.

Hydralazine:

● *Mode of action:* Dilation of arterioles, causing a decrease in peripheral vascular resistance.

● *Dose schedule:* Two to three times per day.

● *Average hypotensive effect:* Decrease of 10% to 15% in mean arterial pressure.

● *Interval between each change of dose:* One to 2 weeks.

● *Advantages:* No interference with sexual function; infrequent orthostatic and exercise hypotension.

● *Adverse effects limiting clinical use:* Reflex increase in heart rate and cardiac output leading to palpitations, headache, angina pectoris or myocardial infarction (concomitant administration of a β-blocker will prevent the increase in heart rate), nausea, nasal congestion, gastrointestinal tract disturbances and drug fever. Long-term use of this drug, particularly when doses are in excess of 200 mg/d, may cause a lupus-erythematosus-like syndrome.

Prazosin hydrochloride: This drug has very recently been introduced to the market, so that experience with its long-term use is limited.

● *Mode of action:* Dilation of arterioles, causing a decrease in peripheral vascular resistance.

● *Dose schedule:* Two to three times per day.

● *Average hypotensive effect:* Decrease of 10% to 15% in mean arterial pressure.

● *Interval between each change of dose:* Two to 3 weeks.

● *Advantages:* Less tachycardia and less increase in cardiac output than with hydralazine.

● *Adverse effects limiting clinical use:* Syncope and loss of consciousness in about 0.8% of patients (usually during the first few days of therapy, but occasionally during long-term administration), orthostatic hypotension, palpitations, drowsiness, dizziness and nausea.

Management of moderately severe hypertension

The higher the blood pressure and the greater the evidence of target organ involvement (heart enlargement, retinopathy or renal impairment), the sooner therapy should be initiated and the more vigorously it should be pursued. It is important to bring the blood pressure towards normal within days to weeks.

Step 1

Drug administration usually starts with the combination of a thiazide-type diuretic and a drug acting on the sympathetic nervous system, most frequently a β-blocker or methyldopa.

Step 2

If the step 1 combination in maximal doses does not reduce the blood pressure to normal an additional drug — a peripheral vasodilator such as hydralazine or prazosin — should be included in the regimen.

Step 3

When the step 2 drugs prove to be ineffective, one of the guanidine derivatives should be added to the regimen. These compounds, guanethidine, bethanidine and debrisoquine, are potent antihypertensive agents for oral use. The action of the three drugs is similar, and selection is generally a matter of personal preference, but most of the reported experience has been with guanethidine.

● *Mode of action:* Depletion and prevention of release of noradrenaline at adrenergic nerve terminals.

● *Dose schedule:* Guanethidine once a day; bethanidine and debrisoquine twice a day.

● *Interval between each change of dose:* Two to 4 weeks.

● *Average hypotensive effect:* Decrease of 15% to 20% in mean arterial pressure with the patient upright.

● *Advantages:* Long duration of action.

● *Adverse effects limiting clinical use:* Severe postural and exertional hypotension, more prominent in the morning and aggravated by vasodilation (due to alcohol or exercise) or plasma volume depletion (concomitant use of a β-blocker can further aggravate postural hypotension), bradycardia, diarrhea, failure of ejaculation, nasal stuffiness, weakness and fatigue.

Management of severe hypertension

Patients with an established diastolic blood pressure of 130 mm Hg or greater before treatment may require urgent treatment. Frequently the use of a diuretic and a drug inhibiting sympathetic nervous activity in addition to bed rest will reduce the diastolic pressure to less than 130 mm Hg within 24 hours. A vasodilator can be added if this has not happened. Guanethidine is added to

the regimen if the above combination does not reduce the blood pressure towards normal within a few days. The timing of the initiation of this combined therapy must depend not only on the level of blood pressure but also on the presence of complications of hypertension.

Patients in this group may require hospitalization. In those with heart failure, encephalopathy or progressive renal insufficiency the blood pressure should be lowered towards normal within minutes to hours. The blood pressure must be brought down promptly but not precipitously towards normal, especially in the elderly. The persistence of uncontrolled blood pressure at these levels can lead to irreversible reduction in organ function. The rapidity and degree of blood pressure lowering should be gauged to maintain adequate perfusion of the vital organs, particularly the brain. For example, in the presence of stroke in evolution, excessive blood pressure lowering should be avoided; a goal blood pressure of 160/100 mm Hg would be more appropriate, and drug therapy should be reduced if stroke symptoms or signs increase in severity. For other patients requiring hospitalization, drugs such as diazoxide or sodium nitroprusside may be administered parenterally under continuous medical supervision.

What if the therapeutic goal is not reached?

If the treatment goal is not achieved, the physician should reexamine the situation to establish:

1. That the patient is complying with the prescribed antihypertensive regimen. If he or she is not, steps should be taken to improve compliance.

2. That the patient is not ingesting an excessive quantity of sodium chloride in his or her diet, or drugs that compete with the prescribed agents (e.g., some cold remedies, antidepressant agents and oral contraceptives).

3. That disease of the vascular or endocrine system or kidneys is not interfering with the efficacy of the prescribed agents. Occasionally effects of the antihypertensive drugs limit their antihypertensive potency.

4. That the prescribed regimen is potent enough and that the doses are sufficient. Dose–response relations should be tested in each patient.

5. That consideration is given to referral of the patient to practitioners or clinics specializing in the treatment of severe refractory essential hypertension.

Comments

Individuals over 65 years of age tolerate antihypertensive medications poorly. Target tissue damage, particularly vascular insufficiency of the heart and brain, often limits treatment. The benefits of therapy in elderly individuals with mild to moderate hypertension are still unknown. Practitioners should be less aggressive in trying to reduce the blood pressure to normal in this group than in younger individuals.

Once the need for it has been established, therapy will usually be required for life. Occasionally a reduction of dosage or of number of medications may be attempted with careful observation of blood pressure control. In some individuals 4 to 6 months may pass before a change in blood pressure is noted after a change in the drug regimen.

The recommendations contained in this article have been made with the aim of improving control of blood pressure in hypertensive patients. However, the need for individualized approaches to the timing and direction of diagnostic tests and therapy should be kept in mind when following these guidelines. The maintenance of blood pressure levels that are close to normal should be achieved with minimal doses, adverse effects and inconvenience to ensure as normal a life as possible for the patient. Only such treatment is likely to be acceptable.

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