

Drug Treatment of Hypertensive Urgencies and Emergencies

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Although systemic hypertension is a common clinical condition, hypertensive emergencies are distinctly unusual in clinical practice. There are some situations, however, that qualify as hypertensive emergencies or urgencies. It is important, therefore, to diagnose these conditions because immediate treatment of severe hypertension is indicated. The diagnosis of hypertensive emergencies depends on the consideration of the clinical manifestations as well as the absolute level of blood pressure. Depending on the target organ that is affected, manifestations of hypertensive emergencies can be quite profound, yet variable. Thus, the physician has to make an accurate clinical diagnosis properly to render appropriate therapy. Fortunately, effective drug therapy is available to decrease blood pressure quickly in hypertensive emergencies. Physicians should be familiar with the pharmacologic and clinical actions of drugs that are used in the treatment of hypertensive emergencies. With proper clinical diagnosis, hypertensive emergencies can be treated successfully and the complications can be prevented with timely intervention. This review discusses the treatment of hypertensive emergencies in general and the therapeutic role of fenoldopam in particular.

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Although any form of hypertensive disorder may be complicated by the development of hypertensive crisis, the main determinants are the level of blood pressure and the clinical manifestations rather than the cause of the hypertension.^{1,2} One feature in the development of certain forms of hypertensive crises is the abruptness with which the blood pressure increases because this factor seems to be more important than the absolute level of blood pressure. In some (but not all) clinical circumstances, immediate reduction of blood pressure is indicated not because of its absolute level but because the coexisting complications (eg, aortic dissection, renal failure, acute left ventricular failure) may make any degree of hypertension dangerously high.

Cause

Hypertensive crises are by tradition categorized into emergencies and urgencies (Tables 1 and 2) but this distinction is arbitrary. Hypertensive emergencies carry a dismal prognosis unless the blood pressure level is reduced immediately; hypertensive urgencies, on the other hand, may pose less immediate danger. Hypertensive emergencies are considered

conditions in which the blood pressure should be reduced in a matter of few hours, whereas in hypertensive urgencies the blood pressure reduction can be accomplished in several hours or days. Unfortunately, there is no concrete level of blood pressure that separates a hypertensive emergency from an urgency; it is the clinical presentation that allows the physician to make such a distinction. The complications of hypertensive crisis are preventable if the treatment is rendered quickly and properly.^{3,4}

Accelerated and Malignant Forms of Hypertension

Although the term *malignant hypertension* probably is used imprecisely, the most striking characteristic pathology of accelerated/malignant hypertension is the presence of vascular lesions in the kidney (and in other target organs). Accelerated hypertension is identified clinically by the presence of severe retinopathy with exudates, hemorrhages, and arteriolar spasm, but without papilledema. Malignant hypertension can be considered an extension of the accelerated form for all practical purposes and is distinguished by the presence of papilledema. Both the accelerated and malignant forms of hypertension are associated with severe vascular injury to the kidney and other target organs. The clinical expressions of accelerated and malignant hypertension are listed in Table 3.

The blood pressure level in malignant hypertension is usu-

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Table 1 Some Examples of Hypertensive Emergencies

Accelerated/malignant hypertension
Hypertensive encephalopathy
Acute left ventricular failure
Acute aortic dissection
? Intracranial hemorrhage
Pheochromocytoma crisis
Monoamine oxidase inhibitor and tyramine interaction
Eclampsia
Substances/drug-induced acute hypertension

ally very high, with diastolic levels often exceeding 130 to 140 mm Hg, but the degree of blood pressure increase is not the only, or a reliable, criterion. It is the extent of vascular injury that determines the nature of malignant hypertension. Severe headache is a common symptom. Generally, the headache is occipital in location and may be more intense in the morning. Patients with malignant hypertension may report visual symptoms ranging from blurring to blindness; drowsiness and altered mental status are common. Congestive heart failure can be an occasional presenting feature of malignant hypertension as a direct consequence of left ventricular dysfunction or caused by volume retention from associated renal failure. Azotemia is a common feature of malignant hypertension and may be associated with proteinuria. Renal function deteriorates rapidly without immediate therapeutic intervention. Even with treatment, renal function may not recover in some patients.

Patients with accelerated/malignant hypertension should be treated in the hospital. Preferably, the patients should be treated in an intensive care unit; if there is no significant target organ dysfunction, they may be managed on the hospital floor with close supervision.

Although parenteral therapy is used widely in the initial treatment of malignant hypertension, various oral therapies also can be used successfully. Angiotensin-converting enzyme (ACE) inhibitors, minoxidil, clonidine, prazosin, labetalol, and nifedipine, all have been used for the initial treatment of malignant hypertension. The choice between oral and parenteral therapy depends on the monitoring facilities, condition of the patient, and coexisting complications.

Hypertensive Encephalopathy

Hypertensive encephalopathy is an uncommon but serious complication of severe hypertension.⁴ Although encephalop-

Table 2 Some Examples of Hypertensive Urgencies

Accelerated/malignant hypertension*
Severe hypertension associated with coronary artery disease
Severe hypertension in the organ transplant patient
Preoperative hypertension
Hypertension associated with burns
Severe, uncontrolled hypertension

*Also can be considered an emergency on the basis of acute target organ dysfunction.

Table 3 Clinical Features of Accelerated and Malignant Hypertension

Marked increase of blood pressure
Malaise, weight loss
Headache
Retinopathy
Renal failure (azotemia, proteinuria, hematuria, and so forth)

athy occurs mainly in patients with chronic uncontrolled or malignant hypertension, it also can complicate sudden hypertension of short duration. Hypertensive encephalopathy should be diagnosed and treated rapidly because it carries a poor prognosis if untreated. The clinical manifestations of hypertensive encephalopathy are caused not only by the severity of blood pressure increase, but also by the abrupt onset of hypertension in a previously (relatively) normotensive individual. Hypertensive encephalopathy occurs more frequently against the background of renal insufficiency than when the kidney function is normal. The full clinical manifestations of hypertensive encephalopathy may take 12 to 48 hours to evolve.

Clinical features of hypertensive encephalopathy are listed in Table 4. Severe generalized headache is a prominent symptom. Symptoms such as confusion, somnolence, and stupor may appear simultaneous with or after the onset of headache. The patient may be quite restless during the initial stages of the syndrome. Other clinical features may include projectile vomiting, visual disturbances ranging from blurring to frank blindness, and transient focal neurologic deficits. In children, generalized or focal seizures may dominate the clinical presentation.

On physical examination, the blood pressure invariably is increased but there is no fixed level of blood pressure above which encephalopathy is likely to occur. The fundi reveal generalized arteriolar spasm with exudates/hemorrhages. Papilledema can be present in most patients with this complication.

Patients with poorly controlled hypertension who present with severe headache, altered mental status, papilledema, and variable neurologic deficits, may have hypertensive encephalopathy, which, of course, must be separated from other acute neurologic complications of hypertension such as cerebral infarction or hemorrhage and uremic encephalopathy. The only definitive way to confirm the diagnosis of hypertensive encephalopathy is prompt response of the patient's condition to immediate antihypertensive therapy.

Once hypertensive encephalopathy is suspected, the blood pressure should be decreased quickly to lower levels; yet the

Table 4 Some Features of Hypertensive Encephalopathy

Marked increase of blood pressure
Headache
Nausea, vomiting
Papilledema
Visual complaints

diastolic blood pressure probably should remain at or slightly greater than 100 mm Hg. Rapid treatment of severe hypertension produces prompt, dramatic, and significant relief of symptoms of hypertensive encephalopathy.^{5,6} The most important goal of therapy is to prevent permanent neurologic damage, and thus blood pressure should be monitored closely to avoid decreasing it too quickly or decreasing it to a level that is too low. In this regard, the placement of an intra-arterial catheter for continuous blood pressure monitoring is often very useful.

Severe Hypertension and Stroke Syndromes

Patients with acute cerebrovascular (stroke) syndromes and severe hypertension pose a challenging therapeutic dilemma. When intracerebral pressure increases as a result of hemorrhage or thrombotic infarction, cerebral blood flow may no longer be under normal autoregulation. Therefore, a reduction in the systemic blood pressure conceivably may compromise further the cerebral blood flow. On the other hand, persistence of severe hypertension may worsen the stroke process. In many patients with acute stroke, initial (reflexive) hypertension may resolve spontaneously within 48 hours. There are no definitive data in the literature that provide the practicing physician with a standard guide to manage these patients.

No absolute guidelines can be given about the management of hypertensive crises occurring in patients with cerebrovascular accidents. Based on the pathogenesis of these conditions, and especially if there is intracerebral hemorrhage, it is advisable to reduce the blood pressure to near-normal levels yet to a degree that will not compromise cerebral function. If there is evidence of progression of the disease or worsening of the neurologic manifestations, then the clinician may need to pause and reassess the therapeutic approach. Precautions should be taken to avoid hypotension in these patients and it is advisable not to lower the diastolic blood pressure to less than 100 mm Hg. Generally, the reduction should be no more than 20% of the baseline blood pressure level.

Acute Aortic Dissection

Of the symptoms listed in Table 5, severe pain is the most frequent manifestation of acute aortic dissection.^{7,8} Sometimes, it can be confused with the pain of acute myocardial infarction. There are certain subtle differences between the pain of aortic dissection and that of myocardial infarction. The pain of dissection is abrupt in onset and is quite severe right from the onset, whereas patients with acute myocardial infarction often report a more insidious onset. The pain of myocardial infarction may come and go, whereas aortic dissection pain occurs abruptly and constantly is severe. Certain descriptions such as tearing, lacerating, throbbing, ripping, excruciating, and burning have been used by patients experiencing acute dissection. There is also an occasional sense of impending death in these patients. Once the diagnosis of aortic dissection is suspected, immediate medical therapy

should be implemented pending the confirmatory diagnostic procedures.

As soon as the diagnosis of acute aortic dissection is apparent, the following steps should be undertaken. If the patient is hypertensive then blood pressure should be reduced to near-normal levels with a drug that causes the blood pressure to decrease smoothly rather than drastically. Direct vasodilators that reflexively stimulate the heart and are contraindicated in acute aortic dissection. When considering medical therapy, one should keep in mind that the force and velocity of ventricular contraction and the pulsatile flow are important determinants of the shearing force acting on the aortic wall. Attempts should be made to decrease the force and velocity of ventricular contraction with a suitable drug.

The blood pressure should be reduced to near-normal levels, and one option in this situation would be trimethaphan (if available), which has a smooth action and is effective rapidly. Because this drug is a ganglion-blocking agent, it decreases the neural transmission at the myocardial contractility sites and has a negative inotropic effect; therefore, it decreases the pulsative flow and also blunts the sharpness of the pulse wave generated by the heart. Because trimethaphan is not available widely and because many physicians are not familiar with its use, other therapies should be considered. These include labetalol, a combined α - and β -blocking drug, and the ultrashort-acting β -blocker esmolol in combination with sodium nitroprusside.

Acute Pulmonary Edema

Severe hypertension may cause or precipitate acute pulmonary edema: the higher the blood pressure, the harder the left ventricle must work. Decreasing the workload of the failing myocardium should improve the cardiac function. In acute left ventricular failure, myocardial oxygen requirements increase owing to increased end-diastolic fiber length and high left ventricular volume. This phenomenon could be detrimental particularly in patients with coexisting coronary artery disease. Prompt reduction of blood pressure with a balanced vasodilating agent such as nitroprusside therefore is indicated in this situation. Sodium nitroprusside decreases both preload and postload, with restoration of myocardial function and cardiac output. Although ACE inhibitors, by the virtue of their pharmacologic actions, may be useful in this situation, there is a paucity of clinical experience concerning the acute therapeutic response to ACE inhibition in patients with acute left ventricular failure.

Severe Hypertension Associated With Acute Myocardial Ischemia

Systemic hypertension increases myocardial oxygen consumption by increasing the left ventricular tension. Patients with myocardial infarction and severe hypertension are likely to benefit from blood pressure reduction, but there are no conclusive data to prove that acute treatment is beneficial. Reduction of systemic blood pressure reduces the cardiac work, wall tension, and oxygen demand and thus may limit myocardial necrosis in the early phase of infarction. With a

Table 5 Clinical Features of Acute Aortic Dissection

Severe pain in the chest, intrascapular region, neck, midback, and sacral area
Syncope
Confusional state or headache
Blindness
Hemoptysis
Dyspnea
Nausea and vomiting
Melena or hematemesis

reduction in the postload, the hemodynamic status may improve significantly in acute myocardial infarction.

Pheochromocytoma Crisis

A patient with pheochromocytoma hypertensive crisis may present with dramatic or striking clinical features. The blood pressure is increased markedly during the paroxysm and the patient may have profound sweating, marked tachycardia, pallor, numbness, tingling, and coldness of the feet and hands.⁹ A single attack will last from a few minutes to hours and may occur as often as several times a day to once a month or less.

If pheochromocytoma is suspected, the α -adrenergic-blocking drug phentolamine (if available) should be given in a dose of 1 to 5 mg intravenously, to be repeated in a few minutes if needed. An alternative to phentolamine would be sodium nitroprusside, but the former is more specific. A β -blocking drug may be useful if the patient has a concomitant cardiac arrhythmia, but the administration of β -blocking agents always should be preceded by either phentolamine or phenoxybenzamine. If this is not performed, β -blockade potentially can aggravate the unopposed α -mediated peripheral vasoconstriction. Labetalol, a combined α - and β -receptor-blocking drug, also has been advocated for this condition. But in our experience it is not effective consistently in controlling the clinical manifestations of pheochromocytoma.

Clonidine Withdrawal Syndrome

Abrupt discontinuation of high doses of clonidine may cause a hyperadrenergic state mimicking pheochromocytoma. Clonidine stimulates the α -receptors in the brain stem, thus reducing peripheral sympathetic activity. When clonidine (in high doses) is discontinued abruptly or tapered rapidly, a syndrome has been noted consisting of nausea, palpitations, anxiety, sweating, nervousness, and headache, along with marked increases of blood pressure.

Symptoms of clonidine withdrawal can be managed by reinstatement of clonidine. If there is marked increase of blood pressure and the patient is experiencing symptoms such as palpitations, chest discomfort, and epigastric discomfort, intravenous administration of phentolamine or labetalol may be necessary.

Hypertensive Crisis Associated With Drug and Food Interactions

Patients receiving monamine oxidase inhibitors are at risk for developing hypertensive crisis if they also take drugs such as ephedrine and amphetamines or consume foods containing large quantities of tyramine. In the presence of an inhibitor of monoamine oxidase, tyramine and indirectly acting sympathetic amines escape oxidative degradation, enter the systemic circulation, and potentiate the actions of catecholamines. Sympathomimetic amines such as those contained in nonprescription cold remedies also can provoke this response. Because of the uncommon use of monoamine oxidase inhibitors, this hypertensive reaction is rare.

Cocaine-Induced Hypertensive Crisis

Cocaine use can cause an abrupt sudden increase in the systemic blood pressure and the heart rate, resulting in a hypertensive emergency. Neurohumoral factors triggered by cocaine likely cause intense vasoconstriction, thus increasing the vascular resistance and the blood pressure level. A sudden increase of blood pressure in a previously normotensive individual may precipitate a serious cardiovascular complication; hence, the blood pressure should be decreased rapidly. Thoracic aortic dissection and even spontaneous acute coronary dissection has been reported after cocaine abuse presumably because of the sudden blood pressure increase.^{10,11}

Eclampsia

Eclampsia is a potentially serious cardiovascular complication in a pregnant patient. Although the definitive therapy is delivery of the fetus, the blood pressure should be reduced to prevent neurologic, cardiac, and renal damage. Although other antihypertensive drugs may be effective in reducing the blood pressure, the agent of choice for rapid control of severe hypertension is hydralazine, which has a long record of safety. Animal studies have shown that nitroprusside can cause problems in the fetus; therefore, its use should be reserved for hypertension refractory to hydralazine or methyldopa. The ganglion-blocking drug trimethaphan should be avoided because of the risk for meconium ileus. In pregnancy-induced hypertension, volume depletion may be present and diuretics should be avoided. ACE inhibitors and angiotensin-receptor blockers should be avoided because of possible fetal/placental toxicity. Magnesium sulfate also is used as adjunctive therapy to decrease the convulsions.

General Guidelines to Treat a Patient with Hypertensive Crisis

The need to hospitalize the patient, therapeutic options, and the question of parenteral versus oral therapy depend on the clinical status of the patient and the available facilities.^{12,13} Patients with hypertensive emergencies should be hospitalized, and those with hypertensive urgencies may not always require admission to the hospital. The therapeutic concept

underlying the management of hypertensive emergency is not only to lower the blood pressure quickly but to prevent, arrest, and reverse the target organ damage. Although there are no concrete guidelines as to the degree of desired blood pressure reduction, a reasonable goal for most hypertensive emergencies is to lower the diastolic blood pressure to 100 mm Hg (or to reduce the mean arterial pressure by 20%) over a period of minutes to hours.¹⁴ Although a secondary form of hypertension such as renal artery stenosis or adrenal hypertension may be a causative factor, the immediate goal should be to lower the blood pressure to a safe level instead of launching a diagnostic work-up, which, of course, can be undertaken subsequently.

Parenteral Drugs for Hypertensive Emergencies

Parenteral drugs for rapid control of severe hypertension are listed in Table 6. Among the drugs listed, nitroprusside is used widely. Other drugs also may have a therapeutic role based on the clinical circumstances. The purpose of this discussion is to provide descriptive details about the usefulness and indications for the use of parenteral drugs for rapid control of hypertension and one particular drug, fenoldopam, is covered in some depth because of its possible special effects on the kidney.

Nitroprusside

Sodium nitroprusside is a potent, rapidly acting intravenous drug with a rapid onset and offset of action. The initial infusion rate should be 0.25 $\mu\text{g}/\text{kg}/\text{min}$, which can be increased every 5 minutes until a desired blood pressure level is obtained. Once the desired effect of nitroprusside is achieved, the blood pressure should be monitored continuously. Cyanide toxicity from nitroprusside, although extremely rare, has occurred. Prophylactic infusion of hydroxocobalamin (vitamin B_{12a}) 25 mg/h, has been shown to decrease the cyanide concentration and tissue hypoxia resulting from nitroprusside infusion during surgery, but this compound is not available routinely. Thiocyanate toxicity secondary to nitroprusside is uncommon and occurs only with high doses and in the presence of renal failure. Treatment should be interrupted when the thiocyanate level is close to 10 mg/dL. Monitoring of plasma thiocyanate levels is not mandatory as long as the patient's clinical status is assessed closely and there is adequate renal function. Treatment of thiocyanate toxicity requires discontinuation of the drug and instituting dialysis.

Intravenous Labetalol

Labetalol is a combined α - and β -adrenergic-blocking drug that can be used parenterally or orally for the treatment of hypertensive emergencies. Intravenous labetalol administered as either a continuous infusion or bolus injections reduces the blood pressure promptly because of its rapid onset of action. Controlled smooth reduction in blood pressure may be obtained by continuous infusion of labetalol at the rate of 0.5 to 2 mg/min. Rapid (but not abrupt) decreasing of blood pressure also can be accomplished with bolus injections of labetalol. Labetalol should not be used in patients

who may have a contraindication for the use of β -blockers such as severe heart failure, atrioventricular block, asthma, or chronic obstructive pulmonary disease.

Nicardipine Infusion

Nicardipine is a dihydropyridine calcium antagonist that exerts a prompt hypotensive effect when given intravenously to patients with severe hypertension. Nicardipine infusion is started at 5.0 mg/h, and can be titrated higher gradually to obtain the desired therapeutic effect.¹⁵ Once a stable blood pressure level is reached, further dosage alterations generally are not necessary. Because of its mechanism of action (calcium-channel blockade), nicardipine may be beneficial in preserving tissue perfusion. This property may be advantageous particularly in patients with ischemic disorders. From our clinical experience, we find nicardipine to be a useful option in the immediate management of severe hypertension.

Trimethaphan

Trimethaphan camsylate is a ganglion-blocking agent. It is the drug of choice for the medical treatment of acute aortic dissection. Similar to nitroprusside, trimethaphan should be administered as a continuous intravenous drip, and constant monitoring is necessary, preferably in the intensive care unit. The usual starting dose of the drug should be 1 mg/min titrated to obtain the desired blood pressure level. After prolonged infusion, tachyphylaxis may result from intravascular volume expansion, which can be overcome partially by effective diuretic therapy. Trimethaphan is not available readily for clinical use.

Diazoxide

Diazoxide, no longer used, has a direct relaxant effect on the vascular smooth muscle, causing a rapid decrease in arterial blood pressure.¹⁶ Diazoxide produces a rapid decrease in blood pressure within 1 minute, and the maximum effect is achieved within 2 to 5 minutes. The hypotensive effect of a single injection of diazoxide may last 2 to 15 hours. Smaller bolus injections and slow intravenous infusions of diazoxide for the treatment of severe hypertension have been used with the hope of reducing the dangers of drastic and precipitous decreases in blood pressure. At present, the need to use diazoxide is eliminated completely by the availability of other, much safer, alternative drugs.

Hydralazine

The antihypertensive action of hydralazine results from a direct relaxation of the vascular smooth muscle and is accompanied by reflex increases in stroke volume and heart rate, which can precipitate myocardial ischemia. Intramuscular or intravenous administration of hydralazine results in an unpredictable but definite decrease in blood pressure. In the treatment of hypertensive emergencies, the initial dose should be 10 to 20 mg. The onset of the hypotensive effect occurs within 10 to 30 minutes and its duration of action ranges from 3 to 9 hours. The dose and frequency of administration necessary to control the blood pressure are highly variable. The delayed onset and unpredictable degree of hypotensive effect presents difficulties in titration. For these

Table 6 Parenteral Drugs for Hypertensive Emergencies

Drug	Available Dose	Administration	Onset of Action	Duration of Action	Adverse Effects	Comments
Sodium nitroprusside	0.25–10 $\mu\text{g}/\text{kg}/\text{min}$, maximal dose is no more than 10 min	IV infusion	Within 30 s	1–2 min	Hypotension, nausea, vomiting, muscle twitching, thiocyanide and cyanide intoxication, methemoglobinemia	Most hypertensive emergencies; caution with renal and hepatic insufficiency and high intracranial pressure
Fenoldopam	0.1–0.6 $\mu\text{g}/\text{kg}/\text{min}$	IV infusion	4–5 min	10–15 min	Reflex tachycardia, may increase intraocular pressure, headache, and nausea	Renal insufficiency, perioperative and postoperative control of blood pressure
Nitroglycerine	5–100 $\mu\text{g}/\text{min}$	IV infusion	2–5 min	3–5 min	Headache, nausea, vomiting, tolerance with prolonged use	Coronary insufficiency
Nicardipine	5–15 mg/h	IV infusion	5–10 min	1–4 h	Reflex tachycardia, headache, nausea, vomiting, flushing	Most hypertensive emergencies, caution with heart failure
Hydralazine	10–20 mg IV	IV infusion	10–20 min	4–12 h	Reflex tachycardia, headache, nausea, vomiting, aggravation of angina	Eclampsia, caution with high intracranial pressure
Enalaprilat	10–50 mg IM 1.25–5 mg every 6 h	IV injection IV infusion	10–15 min	6–24 h	Hypotension, renal failure	Acute left ventricular failure
Labetolol	20–80 mg IV bolus every 10 min, 2 mg/min infusion	IV bolus	5 min	3–6 h	Nausea, vomiting, bronchospasm, heart block, orthostatic hypotension	Most hypertensive emergencies except heart failure
Phentolamine	5–10 mg/min	IV infusion IV bolus	1–2 min	3–5 min	Reflex tachycardia, headache	Pheochromocytoma

Abbreviations: IV, intravenous; IM, intramuscular.

reasons, hydralazine therapy only is relevant clinically in the treatment of eclampsia.

Phentolamine

Phentolamine, an α -receptor–blocking agent, is indicated specifically for treating hypertensive crises associated with increased levels of circulating catecholamines. These include pheochromocytoma crisis, certain cases of clonidine-withdrawal syndrome, and crises resulting from monoamine oxidase inhibitor and drug-food interaction. The hypotensive effect of a single intravenous bolus injection is short-lived and lasts less than 15 minutes. Phentolamine is not available easily for unanticipated clinical use.

Nitroglycerin

Nitroglycerin is a weak systemic arterial dilator with a significant effect on large arteries rather than on smaller arteries. Low doses cause venodilation; much higher doses are re-

quired to produce a decrease in systemic blood pressure. Because of its pharmacologic actions, nitroglycerin infusion may be beneficial particularly in patients with coronary artery disease with or without hypertension. Isosorbide dinitrate therapy also has been used for immediate treatment of severe hypertension¹⁷ but its precise role and guidelines on how to use it are not delineated fully.

Enalaprilat

Enalaprilat, by the virtue of its mechanism of action, prevents conversion of angiotensin I to angiotensin II by blocking ACE and thus lowers the blood pressure. Enalaprilat is the only available parenteral ACE inhibitor. For hypertensive emergencies, it is given intravenously at a dose of 0.625 to 1.25 mg over 5 minutes and may be repeated every 6 hours. ACE inhibitors are contraindicated in patients with renal artery stenosis and in pregnant patients. These drugs are valuable,

especially in treating hypertensive emergencies in patients with chronic heart failure.

Fenoldopam

Fenoldopam is the first dopamine-receptor (DA₁) agonist approved for clinical use in the United States. The dopaminergic receptors, DA₁ and DA₂, exert important physiologic actions on various vascular beds. Hence, these receptors have been studied extensively as targets of pharmacotherapy. DA₁ receptors are juxtaposed postsynaptically on the vascular smooth muscle. Stimulation of DA₁ receptors yield beneficial cardiovascular consequences such as systemic and renal vasodilation. Fenoldopam selectively and preferentially stimulates the DA₁ receptor, resulting in vasodilation. Intravenous infusion of fenoldopam results in a dose-related decrease in systemic blood pressure,^{18,19} mainly caused by vasodilation and to a small extent caused by natriuresis. Poor and variable absorption and erratic bioavailability precluded the development of oral fenoldopam; the drug should be given as an infusion, not as a bolus.

Fenoldopam infusion causes a rapid, predictable decrease in blood pressure. The onset and duration of action of fenoldopam and its pharmacokinetics resemble those of nitroprusside. Experimental studies in patients with a moderate degree of hypertension clearly have established its useful antihypertensive effects.²⁰ In severe forms of hypertension (diastolic blood pressure > 120 mm Hg), fenoldopam infusion produces dramatic antihypertensive effects; overall, the efficacy of fenoldopam is similar to that of nitroprusside,²¹ a gold standard drug for rapidly decreasing blood pressure. In contrast to nitroprusside, however, fenoldopam improves renal function parameters acutely such as creatinine clearance and sodium excretion^{22,23}; an increase in renal blood flow also has been shown with fenoldopam.

In hypertensive emergencies, fenoldopam administration causes a rapid, predictable, and desirable decrease in blood pressure. The magnitude of response and the onset of action of fenoldopam depend on the infusion dose (as is the case with nitroprusside). Besides the conventional hypertensive emergencies or urgencies, studies also have confirmed the usefulness of fenoldopam in the management of perioperative hypertension. In this setting, fenoldopam may be more advantageous than nitroprusside because of its possible target organ protection.^{24,25} The potential advantages of this drug over nitroprusside must be weighed against its markedly higher cost.

Fenoldopam and possible renal protection. Dopamine is known to exert beneficial renal effects mediated by preservation (or augmentation) of renal blood flow in clinical situations accompanied by renal impairment. Because of inconclusive and inconsistent results from dopamine on the kidney, considerable interest has been focused on the renal actions of a more selective agonist such as fenoldopam. In contrast to heterogeneous and complex actions of dopamine, the renal actions of fenoldopam are more specific and mediated entirely by DA₁-receptor stimulation. An ideal scenario for favorable renal outcome is for a drug to decrease the renal

vascular resistance, yet maintain (or enhance) renal blood flow and cause physiologic natriuresis and diuresis. Fenoldopam fulfills some of these postulates. Hence, the renal effects of fenoldopam have been studied carefully in normal human beings and in those with impaired renal function with or without hypertension.²⁶⁻²⁸

In the normal patients, fenoldopam infusions (in a dose-related manner) consistently cause a decrease in renal vascular resistance with a simultaneous increase in renal plasma flow, fractional excretion of sodium, and urine flow, while maintaining the glomerular filtration rate. These observations define the favorable physiologic profile of fenoldopam on the kidney.

In hypertensive patients, fenoldopam maintains adequate glomerular filtration rate while increasing the urine flow and sodium excretion. In patients with severe hypertension (average blood pressure > 204/130 mm Hg), fenoldopam (in contrast to nitroprusside) increases the creatinine clearance and sodium excretion rates. Because a highly selective DA₁ agonist such as fenoldopam produces a range of favorable renal effects, there is considerable rationale and basis for its therapeutic role in acute renal failure, contrast-induced nephropathy, cyclosporine-associated nephrotoxicity, perioperative renal protection, and so forth.²⁹⁻³² These actions point to a not yet fully explored potential of fenoldopam in the prevention and management of renal dysfunction of diverse causes. In 1 study,²⁸ prophylactic administration of fenoldopam decreased the risk for radiocontrast nephropathy by 66%, but other studies have been negative. In the absence of a large-scale controlled study performed under rigorous scientific conditions, we cannot conclude definitively that this agent can prevent or treat intrinsic acute renal failure.

Adverse effects. A number of minor adverse effects of fenoldopam are caused by its vasodilatory actions including tachycardia, flushing, and headache.^{24,25} These side effects may appear as the start of fenoldopam infusion and often dissipate.^{22,23} Nonspecific electrocardiographic ST-T changes probably are caused by systemic hemodynamic changes caused by fenoldopam, but not direct cardiac effects. Fenoldopam increases intraocular pressure and thus should be avoided in patients with glaucoma. Although of obvious interest, no adverse interactions have been reported between fenoldopam and other cardiovascular drugs.

Therapeutic significance of fenoldopam. Severe hypertension and hypertensive emergencies or urgencies can cause considerable morbidity and mortality. Even with intervention patients may suffer from residual target organ damage. Although there are several pharmacologic options for immediate control of hypertension, fenoldopam offers a number of conceptual advantages. Although fenoldopam is as effective and as rapidly acting as nitroprusside, its pharmacologic actions on the circulatory parameters and on the kidney offer a distinctive theoretical advantage. In contradistinction to nitroprusside, coronary or cerebral steal phenomenon and thiocyanate toxicity do not occur with fenoldopam. In addition to hypertensive disorders, there is a continuing interest

in the application of fenoldopam therapy in the management and prevention of certain forms of acute renal failure, such as cyclosporine- or contrast-induced nephropathy. Further work remains to be performed in this area.

Role of Concomitant Diuretic Therapy in the Management of Hypertensive Emergencies

Diuretics per se have a limited role in the management of hypertensive emergencies; however, they potentiate the therapeutic response to nondiuretic agents. When the blood pressure does not respond satisfactorily to an adequate dose of the primary agent, adding a diuretic (such as furosemide) may be helpful. Certainly, in volume overload states such as heart failure, concomitant administration of a loop diuretic is indicated for optimal results. Diuretics, however, should not be used routinely in the management of hypertensive crises because prior volume depletion may be present in some patients with severe or complex hypertension. The need for diuretic therapy, therefore, should be individualized on the basis of the hemodynamic and renal function status of the patient.

Oral Drugs for Acute Treatment of Severe Hypertension

Clinical experience has shown that antihypertensive drugs given orally in either single or multiple doses lower the blood pressure immediately in patients with severe hypertension. Obviously, this therapeutic avenue is most suitable for patients with hypertensive urgencies, not emergencies.

Nifedipine

Nifedipine, a calcium-channel blocker, given orally or sublingually, has been shown to reduce the blood pressure rapidly and has been found to be useful in the management of hypertensive crisis.³³ An immediate reduction in blood pressure can be accomplished with sublingual (punctured capsule, or nifedipine liquid drawn out of the capsule with a syringe) or oral administration of the capsules. The drug also is effective when the capsule is bitten and then swallowed. The advantages of nifedipine are rapid onset of action and lack of central nervous system depression. It may cause reflex tachycardia. Because the duration of action of nifedipine is short, patients who receive this drug for hypertensive emergencies should be monitored for several hours to consider re-administration of the drug. An abrupt decrease in the blood pressure induced by nifedipine administration can cause certain adverse effects: symptomatic hypotension, tachycardia, and ischemic events that occasionally are life-threatening. Therefore, the clinical need to use nifedipine capsules urgently should be assessed carefully. In recent years we have not used this drug sublingually at all, but oral administration still is useful in selected patients.

Clonidine

Clonidine therapy has been shown to produce an immediate antihypertensive effect with repetitive dosing. Typically, clonidine loading was accomplished in the emergency room by administering clonidine orally 0.1 mg every hour until the

desired goal was obtained. Clonidine loading as therapy is justifiably decreasing, mostly because of its unfavorable side-effect profile and the availability of better oral agents.

ACE Inhibitors

Captopril, an ACE inhibitor, has been found to be effective in the immediate treatment of severe hypertension and hypertensive crises.³⁴ Captopril decreases the blood pressure promptly without causing tachycardia and thus offers a distinct hemodynamic advantage over direct arteriolar dilators; however, the maximal effect from orally administered captopril may not be attained for as long as 2 hours. On the other hand, there are some reports documenting the effectiveness of sublingual captopril in the treatment of a hypertensive crisis. Because experience with sublingual captopril is rather limited, further data must be generated to define its role in the acute management of hypertensive crisis.

Minoxidil

Minoxidil is a powerful direct vasodilator and has been used successfully in the treatment of refractory or severe hypertension. Because of its relatively rapid onset of action and sustained duration, this drug has been used for the treatment of hypertensive crises. Minoxidil in doses ranging from 2.5 to 10 mg can be given every 4 to 6 hours initially in the treatment of severe hypertension. It works best when given along with a diuretic, and an adrenergic blocker is necessary to counteract the reflex tachycardia.

Oral Labetalol

Labetalol, a combined α - and β -adrenergic blocker, can be administered orally (100-300 mg) in the treatment of hypertensive urgencies. Because of its dual adrenergic blockade, the decrease in blood pressure is not accompanied by reflex tachycardia, which can be beneficial, especially in patients with coronary artery disease.

Summary

Once the hypertensive emergency has resolved and the patient's clinical condition is stable, the physician should look into possible factors that might have contributed to the dangerous increase of blood pressure, such as noncompliance to prescribed therapy or the presence and/or progression of a secondary form of hypertension such as a renal artery stenosis or renal failure. After the patient's condition has stabilized, the physician should discuss long-range and periodic outpatient follow-up plans; close follow-up evaluation is essential for these patients.

The most important decision in the management of hypertensive emergencies is to assess the patient's clinical state and to ascertain whether the patient's condition truly needs immediate reduction of blood pressure. The choice of an oral versus parenteral drug depends on the urgency of the situation, as well as the patient's general condition. The level to which the blood pressure should be lowered varies with the type of hypertensive crisis and should be individualized. The choice of parenteral drug is dictated by the clinical manifestations and concomitant medical problems associated with

hypertensive crisis. There is no predestined level for the goal of acute therapy. Complications of therapy, mainly hypotension and ischemic brain damage,³⁵ can occur in patients given multiple potent antihypertensive drugs in large doses. A relatively asymptomatic patient who presents with severe hypertension, that is, a diastolic blood pressure of 130 to 140 mm Hg, need not be treated with parenteral drugs in our view. These patients should be managed on an individual basis and the usual course would be to intensify or alter the previous antihypertensive therapy. All too often, asymptomatic patients, or those patients without an acute problem, are subjected unnecessarily to immediate needless therapy. A significant immediate change in the patient's blood pressure may be self-gratifying to the physician, but is not indicated for most patients with asymptomatic severe hypertension. The indiscriminate use of drugs such as nifedipine and furosemide should be discouraged strongly. From a pharmacoeconomic point of view, it makes sense to try to prevent a hypertensive emergency rather than to treat it. The prevention of recurrent hypertensive emergencies is of considerable importance, and requires aggressive and sustained control of chronic hypertension in the community.

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