Intravenous therapy for hypertensive emergencies, part 1

DENISE RHONEY AND W. FRANK PEACOCK

Hypertension is a global problem, affecting 50 million people in the United States and 1 billion people worldwide.1,2 In the United States, as many as 60% of adults over age 18 years are either prehypertensive or hypertensive, according to the seventh report of the Joint National Committee on Prevention, Diagnosis and Treatment of High Blood Pressure (JNC-7) guidelines.1-3 The Framingham Heart Study found that individuals who are normotensive at age 55 years have a 90% lifetime risk of developing hypertension.4

Detection, Evaluation, and Treatment of High Blood Pressure. Since the publication of these recommendations, another i.v. antihypertensive agent, clevidipine, became commercially available. The selection of a specific agent should be based on the agent’s pharmacology and patient-specific factors, such as comorbidity and the presence of end-organ damage.

Conclusion. The rapid recognition and initiation of therapy are key to minimizing end-organ damage in patients with hypertensive emergency. Tailoring drug selection according to individual patient characteristics can optimize the management and potential outcomes of patients with hypertensive emergency.

Index terms: Clevidipine; Drugs; Emergencies; Enalaprilat; Esmolol; Fenoldopam; Hydralazine; Hypertension; Hypotensive agents; Injections; Labetalol; Nicardipine; Nitroglycerin; Nitroprusside; Phentolamine


Copyright © 2009, American Society of Health-System Pharmacists, Inc. All rights reserved. 1079-2082/09/0801-1343$06.00.

DOI 10.2146/ajhp080348.p1

Supplementary material is available with the full text of this article at www.ajhp.org.
In general, the multiple agents available for the treatment of hypertensive emergencies rapidly lower BP in patients at imminent risk of or during evolving end-organ damage. The goal of drug therapy is to reduce BP in a controlled and predictable manner, while weighing the potential adverse effects of each drug on an individual basis. Both drug-specific and patient-specific factors must be considered to ensure the selection of an appropriate agent. Drug-specific factors include the drug’s pharmacokinetic parameters and adverse effects. In addition, due to the potential for “overshoot” with agents like nitroprusside, arterial BP monitoring is a requirement for the use of some agents. Cost-effectiveness is another important drug-specific factor and should include consideration of the length of hospital stay, time spent in the ICU, and long-term morbidity. Unfortunately, few studies have rigorously evaluated the cost-effectiveness of pharmacologic agents for the management of hypertensive emergencies. Thus, treatment decisions cannot currently be based on perceived cost-effectiveness. A detailed description of important drug-specific factors of each agent is available in eTables 1 and 2 (accessible online at www.ajhp.org).

Patient-specific factors that must be considered when selecting an appropriate drug and dose include patient age, race, pregnancy status, and volume status and the presence of end-organ disease and other comorbidities. In general, elderly patients may be more responsive to the hypotensive effects of these agents; for this reason, it is a good practice to start with a lower dose or infusion rate of these agents in patients over age 65 years. Race may be an important consideration for the use of many antihypertensives. For example, i.v. enalaprilat is most effective in treating hypertension associated with high renin levels. Thus, populations with traditionally low renin levels (e.g., African Americans) may experience smaller BP reductions than patients with high renin values. Similarly, patients with high renin levels may have large and rapid decreases in BP and should be closely monitored. Both hepatic and renal function status are important considerations with agents that rely on these organ systems for elimination or whose toxic metabolites may need elimination, such as with sodium nitroprusside.

**Clinical pharmacology of i.v. antihypertensives**

**Calcium-channel blockers.** Calcium-channel blockers (CCBs) are a heterogeneous class of drugs used in the treatment of hypertension, coronary artery disease (CAD), and dysrhythmias. The available CCBs are categorized into the three structural classes: dihydropyridines (e.g., nicardipine, clevidipine), phenylalkylamines (e.g., verapamil), and benzo-thiazepines (e.g., diltiazem).
Although six types of calcium channels exist, the L-type and T-type channels are relevant to cardiovascular disease. The T-type channel may be associated with significant drug interactions and the potential for life-threatening arrhythmia. The other channels—N-type (pain management), P-type and Q-type (migraine or epilepsy), and R-type (diabetes mellitus)—are not influenced by the CCBs discussed in this article and are the subject of ongoing clinical investigation.

L-type CCBs inhibit the influx of extracellular calcium ions through calcium channels located in cellular membranes of myocardial, vascular smooth muscle, or cardiac conduction system cells and into intracellular organelles. The loss of extracellular calcium ion influx inhibits intracellular phosphodiesterase, which raises guanosine monophosphate (GMP) levels, inhibiting vascular smooth muscle contractility, myocardial contractility, and cardiac conduction to different degrees, depending on the particular drug’s affinity for a particular L-type channel receptor and the type of cell affected. The dihydropyridines (nicardipine and clevidipine) are selective for vascular smooth muscle over myocardium in the order of cerebral, coronary, peripheral muscle, and renal vascular smooth muscle, with little if any activity in cardiac muscle or the sinoatrial node; thus, they have little effect on heart rate and no effect on myocardial contractility. The vascular smooth muscle relaxation induced by the dihydropyridines causes vasodilation and a reduction of systemic BP. In contrast, diltiazem and verapamil have a predilection for the cardiac conduction systems and myocardial calcium channels. Intracoronary administration of diltiazem and verapamil decreases myocardial contractility and induces conduction system abnormalities.

Nicardipine. Nicardipine may have unique benefits in cerebrovascular disease based on its pharmacologic profile. It crosses the blood-brain barrier and acts to vasorelax cerebrovascular smooth muscle. At the acidic pH of ischemic cerebral tissue, nicardipine is almost 100% protonated, allowing for rapid accumulation in ischemic tissue, localized vasodilation, and a reduction in vasospasm seen in patients with acute subarachnoid hemorrhage. Although nicardipine is a cerebral vasodilator, it dilates small-resistance arterioles, so there are no significant changes in intracranial volume or intracranial pressure (ICP). Nicardipine also reduces cardiac ischemia, increases stroke volume and coronary blood flow, and has a favorable effect on myocardial oxygen balance. However, nicardipine is contraindicated in patients with advanced aortic stenosis. The most common adverse events associated with nicardipine are related to vasodilation and include headache, hypotension, nausea, vomiting, and tachycardia.

For hypertensive emergencies, the initial i.v. infusion rate for nicardipine is 5 mg/hr, increasing by 2.5 mg/hr every 5 minutes to a maximum of 30 mg/hr, adjustable as needed. Once the target BP is achieved, downward adjustment by 3 mg/hr should be attempted as tolerated. Its onset of action is 5–15 minutes, and the duration of action is 4–6 hours. Steady-state concentrations are achieved after 24–48 hours of continuous infusion. Nicardipine’s terminal elimination half-life is 14.4 hours. The steady-state pharmacokinetics of nicardipine are similar between elderly hypertensive patients (over age 65 years) and young healthy adults.

Clevidipine. Clevidipine, the first third-generation dihydropyridine CCB, recently received marketing approval in the United States. Clevidipine specifically dilates arterioles and reduces afterload without affecting cardiac-filling pressures or causing reflex tachycardia. Clevidipine has a rapid onset (2–4 minutes) and offset of action (5–15 minutes). It undergoes rapid ester hydrolysis by arterial blood esterases to form inactive metabolites. This unique metabolism terminates the action of clevidipine, independent of renal or hepatic functional status. The initial phase half-life (measured in cardiac surgery patients) is less than one minute, and its terminal half-life is approximately four minutes.

Clevidipine has the potential to protect against organ reperfusion injury through its ability to hamper oxygen free radical-mediated toxicity and cellular calcium overload and to augment endothelial nitric oxide bioavailability via antioxidative actions. Thus, clevidipine may diminish the severity of low-flow myocardial ischemia, preserve coronary endothelial function, reduce infarct size, and maintain renal function by preserving splanchnic blood flow.

The starting dose of clevidipine is 1–2 mg/hr. The dose can be doubled every 90 seconds until BP approaches the target, then increased by less than double every 5–10 minutes. There is limited experience with doses higher than 32 mg/hr or any dose given longer than 72 hours. This agent is insoluble in water and is commercially available in a lipid emulsion. Clevidipine is contraindicated in patients with allergies to soybeans, soy products, eggs, or egg products. Clevidipine is also contraindicated in patients with defective lipid metabolism, such as pathological hyperlipemia, lipid nephrosis, or acute pancreatitis, if it is accompanied by hyperlipidemia. Due to lipid-load restrictions, no more than 1000 mL or an average of 21 mg/hr of clevidipine infusion is recommended per 24-hour period. Clinicians must account for the calories infused from the lipid emulsion and adjust the nutrition regimen as needed and monitor triglyceride levels during prolonged administration. Since this
Nitric oxide vasodilators. Sodium nitroprusside. Sodium nitroprusside is a nitric oxide donor. Free-radical nitric oxide activates endovascular guanylyl cyclase, causing myosin dephosphorylation and vascular smooth muscle relaxation. The drug acts on arteriolar and venous smooth muscle, reducing both preload and afterload. However, in patients with CAD, the theoretical “coronary steal” (i.e., redistribution of oxygenated blood away from nonvasodilating areas of ischemia toward nonischemic myocardium with dilated coronary arteries) results in reduced coronary perfusion pressure. A recent study that compared the cerebral hemodynamic effects of sodium nitroprusside with those of labetalol in patients with malignant hypertension suggested that a “cerebral steal-like effect,” with a preferential blood flow to the low-resistance systemic vascular bed rather than the cerebral vascular bed, was found with sodium nitroprusside. Unpredictable shifts in BP are often seen in patients with hypovolemia or diastolic dysfunction due to the effects of venodilation.

There are potential concerns with the use of sodium nitroprusside in patients with brain injury and subsequent altered intracranial compliance (alterations in intracranial vault volume). Case reports and studies have shown a direct correlation between increased ICP and sodium nitroprusside infusion. Information regarding the effect of sodium nitroprusside on cerebral blood flow is conflicting, with many studies conducted in the operating suite while patients were under the influence of various anesthetic regimens that also affect cerebral blood flow. Unlike the dihydropyridine CCBs, sodium nitroprusside dilates large-capacitance vessels, including cerebral vessels that may increase cerebral blood volume, leading to an increase in ICP and a subsequent decrease in cerebral perfusion pressure (calculated by subtracting ICP from MAP). Patients with altered cerebral autoregulation or intracranial compliance may be extremely susceptible to the sudden variations in MAP and cerebral vasodilation induced by sodium nitroprusside.

Although vasodilators are generally contraindicated in aortic stenosis, sodium nitroprusside is safe in selected patients with aortic stenosis and left ventricular systolic dysfunction. The drug should not be administered to patients with hypertensive emergency in the setting of acute myocardial infarction (MI), as it was associated with increased mortality when administered within nine hours of the onset of chest pain in patients with acute MI and elevated left ventricular filling pressure.

The initial dose of sodium nitroprusside is 0.3–0.5 μg/kg/min, with increases in increments of 0.5 μg/kg/min to reach the desired hemodynamic effect. The duration of treatment should be as short as possible, and it is best to avoid doses exceeding 2 μg/kg/min. The dosage requirement in elderly patients is lower than in younger patients. The exact mechanism of this increased sensitivity is largely unknown but is hypothesized to be related to diminished baroreceptor reflex activity, resistance of cardiac adrenergic receptors to catecholamine stimulation, or variations in the direct vasodilating effects of sodium nitroprusside. It has an immediate onset and a duration of effect of two to three minutes. Intravenous BP monitoring is recommended when using sodium nitroprusside because of the potential for “overshoot.” In addition, tachyphylaxis may develop while using this agent.

A major concern regarding the use of sodium nitroprusside is the accumulation of toxic metabolites. Cyanide toxicity results in cellular hypoxia and is clinically manifested by irreversible neurologic changes and cardiac arrest. Sodium nitroprusside comprises a ferrous ion centered complexed with five cyanide moieties and a nitrosyl group and is 44% cyanide by weight. Each molecule releases five cyanide radicals, which may react with methemoglobin and produce cyanomethemoglobin. Normal methemoglobin concentrations can bind the cyanide released from 18 mg of sodium nitroprusside. The total dose of sodium nitroprusside required to cause 10% methemoglobinemia is >10 mg/kg (>10 μg/kg/min for more than 16 hours). Because the remaining cyanide radicals are converted to thiocyanate by transulfuration in the liver and excreted by the kidneys, the drug should be avoided whenever possible in patients with hepatic or renal failure. Normally, adults can detoxify 50 mg of sodium nitroprusside using existing stores of sulfur, but malnutrition, surgery, diuretic use, or other factors can reduce this capacity. Because free cyanide radicals may bind to and inactivate tissue cytochrome oxidase, thereby preventing oxidative phosphorylation, an increase in cyanide concentrations may also cause tissue anoxia, anaerobic metabolism, and lactic acidosis. Patients receiving sodium nitroprusside who show subsequent central nervous system dysfunction, cardiovascular instability, and increasing metabolic acidosis should be assessed for cyanide toxicity, and sodium nitroprusside should be discontinued. Monitoring for cyanide toxicity is difficult. The use of the red blood cell cyanide level is a sensitive method but not readily
available at many institutions, limiting its everyday clinical utility, which leaves the clinician to assess for metabolic acidosis and conduct a clinical examination.

For sodium nitroprusside infusions of 24–10 μg/kg/min or durations longer than 30 minutes, thiosulfate can be coadministered at a 10:1 sodium nitroprusside to thiosulfate ratio to avoid cyanide toxicity, particularly during surgical procedures that require intraoperative hypotension for longer than 30 minutes. As an alternative, hydroxycobalamin (vitamin B₁₂) received marketing approval in 2006 from the Food and Drug Administration (FDA) for the treatment of known or suspected cyanide poisoning. The starting dose is 5 g (available as 2.5-g vials) administered by i.v. infusion over 15 minutes. The safety of coadministration with other cyanide antidotes has not been established. Because of its dark red color, the two most common adverse reactions reported with sodium nitroprusside were chromaturia (red urine) and erythema (skin redness). Hydroxycobalamin also has the potential to cause photosensitivity and can interfere with colorimetric determinations of certain laboratory values. Hydroxycobalamin is unstable and should be stored in a dry place and protected from light. Cyanocobalamin (vitamin B₁₂) is completely ineffective as a cyanide antidote.

Thiocyanate can cause toxicity, although it is 100-fold less toxic than cyanide. It is eliminated by renal excretion, with a half-life of 3–7 days. Sodium nitroprusside infusions of 2–5 μg/kg/min for 7–14 days may be needed to generate thiocyanate toxicity. Nonspecific symptoms of thiocyanate toxicity include fatigue, tinnitus, nausea, and vomiting; clinical signs include hyperreflexia, confusion, psychosis, and miosis.

Nitroglycerin. Nitroglycerin is primarily a venodilator, though dilation of arterial smooth muscle also occurs with high doses. Once nitroglycerin is converted to nitric oxide, it activates guanylate cyclase and stimulates the production of cyclic GMP (cGMP). This produces smooth muscle relaxation, mainly in the venous system, and reduces myocardial preload. In volume-depleted patients, typical of hypertensive emergencies other than APE, a reduced myocardial preload reduces cardiac output and is undesirable in patients with compromised myocardial, cerebral, or renal perfusion. Severe hypotension and reflex tachycardia have been reported in volume-depleted patients within minutes of initiating nitroglycerin infusion.

For the treatment of hypertension, the initial dose of nitroglycerin is 5 μg/min by i.v. infusion. The dose may be increased in increments of 5 μg/min every 3–5 minutes to a maximum rate of 20 μg/min. If the BP response is inadequate at 20 μg/min, the dose may be increased by 10 μg/min every 3–5 minutes, up to a maximum rate of 200 μg/min. When a partial response is achieved, dosing increments are made more carefully. Drug onset is within 2–5 minutes, and the duration of action is 5–10 minutes, with a half-life of 1–3 minutes. Tolerance to the hemodynamic effects of nitroglycerin may limit its clinical usefulness. Headache is the most common adverse effect, and methemoglobinemia is a rare complication of prolonged nitroglycerin therapy. Administration of low-dose nitroglycerin (=60 μg/min) as an adjunct to other i.v. antihypertensive therapy may be beneficial for patients with hypertensive emergencies associated with acute coronary syndromes or APE.

**Hydralazine.** Hydralazine is a peripheral vasodilator that causes relaxation of arteriolar smooth muscle by inhibiting calcium ion release from the sarcoplasmic reticulum. The specific mechanism of action is not known, but proposed mechanisms include blocking the release of inositol trisphosphate-induced calcium and reducing calcium turnover. The vasodilation reduces cardiac afterload and may improve cardiac function in patients with heart failure. There is also evidence of a direct myocardial effect from increased sarcocell calcium influx. This may be partly due to the stimulation of β-adrenergic receptors. Other proposed mechanisms of action include membrane hyperpolarization, generation of nitric oxide, elevation of intracellular cGMP, or inhibition of oxidase formation.

Recent evidence suggests that hydralazine induces hypoxia-inducible factor-1α, which upregulates multiple endothelial cell growth factors that induce cGMP. Small increases in ICP associated with hydralazine use have been reported in patients with defective or absent cerebral autoregulation. Hydralazine causes a reflex stimulation of the sympathetic nervous system that can result in increases in pulse rate and ICP; however, this effect can be blunted by coadministration of β-receptor antagonists.

The initial dose of hydralazine in acute hypertension is a 10-mg bolus via slow i.v. infusion (maximum initial bolus dose, 20 mg) every 4–6 hours as needed. Repeated bolus doses via slow i.v. infusion generally do not exceed 20 mg, although they may be increased to 40 mg. BP begins to decrease within 10–30 minutes, and the fall lasts 2–4 hours. Hydralazine may also be given intramuscularly. Onset of action after i.v. administration is 10–20 minutes, with a duration of 1–4 hours. While hydralazine’s half-life is 1.5 hours, its effect on BP generally persists for 2–4 hours. However, a pharmacologic effect on BP exceeds 100 hours. The prolonged effect may be due to active metabolites, tissue binding in the arteriolar wall, or a sustained effect on endothelium-derived relaxing factor. The unpredictability of...
response and prolonged duration of action do not make hydralazine a desirable first-line agent in most patients with hypertensive emergencies. As with all i.v. antihypertensives, the transition to oral therapy should begin as soon as possible after BP stabilization.

Adrenergic-receptor antagonists. Phentolamine. Phentolamine, a competitive antagonist of peripheral \( \alpha_1 \)- and \( \alpha_2 \)-receptors, is generally used to treat hypertensive emergencies induced by catecholamine excess, such as pheochromocytoma, interactions between monoamine oxidase inhibitors and other drugs or food, cocaine toxicity, amphetamine overdose, or clonidine withdrawal.1,64,65 Phentolamine is given as an i.v. bolus dose of 5–15 mg. The onset of action is 1–2 minutes, with a duration of 10–30 minutes.1 It should be used cautiously in patients with CAD, as it can induce angina or MI.66 Tachycardia, flushing, and headache are also common adverse effects.1 Compensatory tachycardia is managed with an i.v. \( \beta \)-blocker. Esmolol. Esmolol is a \( \beta_1 \)-adrenergic antagonist with a rapid onset and a very short duration of action. Its negative inotropic and chronotropic profiles and \( \beta_1 \)-cardioselectivity pair well with a direct-acting \( \alpha \)-adrenergic vasodilator such as phentolamine, since esmolol has no direct vasodilatory actions.

Typically, the drug is given as a 0.5–1.0-mg/kg loading dose over 1 minute, followed by a 50-\( \mu \)g/kg/min infusion. For additional dosing, the bolus dose is repeated and the infusion increased in 50-\( \mu \)g/kg/min increments as needed to a maximum of 300 \( \mu \)g/kg/min.14,67 The onset of action is approximately 1 minute.14 The drug is rapidly metabolized by erythrocyte esterases, with a terminal half-life of 9 minutes and a duration of action of 10–20 minutes.67,68 Concomitant anemia may prolong esmolol’s short duration of effect due to the metabolic pathway.

One of the major indications for esmolol is to decrease the sympathetic discharge seen with severe postoperative hypertension, when cardiac output, heart rate, and BP are increased.69-74 Esmolol is indicated for perioperative hypertension and is safe in the setting of myocardial ischemia or infarction.75 Patients should be monitored for bradycardia, which may be more problematic in the elderly, who may be more sensitive to the bradycardic effects. If bradycardia occurs, the effects of esmolol on heart rate are eliminated within 20 minutes after drug discontinuation. Esmolol reduces cardiac index and may worsen or exacerbate symptoms in patients with heart failure.1,76 Although esmolol is cardioselective, patients with reactive airway disease should be monitored closely, even though several studies have shown esmolol to be well tolerated in patients with pulmonary disease.76 Current contraindications to the use of esmolol include concurrent \( \beta \)-blocker therapy, bradycardia, and decompensated heart failure.

Massive accidental overdosages of esmolol due to dilution errors, resulting in both fatalities and permanent disability, have been reported.77 Bolus doses in the range of 625 mg to 2.5 g (12.5–50 mg/kg) have been fatal. Premixed injection solutions are available and may help reduce dosage errors.

I.V. \( \beta \)-blockers, often used as monotherapy for ischemic CAD, will potentiate sympathomimetic, drug-induced, coronary and peripheral arterial vasoconstriction if given unopposed.78 Unopposed \( \beta \)-blockade may induce \( \alpha \)-storm (i.e., unopposed \( \alpha \)-stimulation), with increased drug-induced toxicity and physiological decapsulation that may lead to death.11 Labetalol. Labetalol is a combined \( \alpha_1 \)- and nonselective \( \beta \)-adrenergic blocker. Its pharmacodynamic action is primarily mediated by \( \beta \)-blockade, with an \( \alpha \)- to \( \beta \)-receptor activity ratio of 1:7 when given intravenously.7 The \( \alpha_1 \)-blocking component minimizes reductions in cardiac output observed with \( \beta \)-blockers alone.7 Unlike esmolol, labetalol reduces systemic vascular resistance without reducing total peripheral blood flow. Labetalol has very little effect on cerebral circulation and is thus not associated with increased ICP in the normal brain.79 The drug may be particularly useful when the hypertensive emergency is caused by hyperadrenergic syndromes.65 Because it is a nonselective \( \beta \)-blocker, labetalol is contraindicated in patients with reactive airway disease or chronic obstructive pulmonary disease. It may worsen or exacerbate heart failure and should not be used in patients with second- or third-degree atrioventricular block or bradycardia.1,66

A loading dose of labetalol 20 mg i.v. typically precedes either an infusion or ongoing bolus doses of labetalol. Labetalol as a single bolus dose has an onset of action of 2–5 minutes, with a duration of action lasting 2–4 minutes.14 Incremental doses of 20–80 mg at 10-minute intervals continue until the target BP is reached. An infusion of 1–2 mg/min, adjusted until the target BP is achieved is an effective alternative regimen. Bolus-dose injections of 1–2 mg/kg have produced precipitous decreases in BP and should therefore be avoided.80 The duration of effect with repeated sequential bolus doses or infusions is 2–4 hours, with an elimination half-life of 5.5 hours.81 Fenoldopam. Fenoldopam is a peripheral dopamine type 1 (D\(_1\)) agonist. It has no activity on dopamine type 2 receptors. Stimulation of postsynaptic D\(_1\) receptors causes vasodilation of peripheral arteries and the renal and mesenteric vasculature, lowering BP and total peripheral resistance while preserving renal blood flow.82 Although fenoldopam increases intraocular pressure, very little information is available regarding
the effects of fenoldopam on the cerebral vasculature, so it should be avoided in patients at risk for increased intraocular pressure and increased ICP. The effects of this agent on renal function were assessed in a meta-analysis involving 1290 patients from 16 randomized controlled trials evaluating the renal protective properties of fenoldopam in a variety of settings. Fenoldopam was associated with a lower risk of the need for renal replacement therapy (odds ratio [OR], 0.54; 95% confidence interval [CI], 0.34–0.84; \( p = 0.007 \)) in hospital death (OR, 0.64; 95% CI, 0.45–0.91; \( p = 0.01 \)), and acute kidney injury (OR, 0.43; 95% CI, 0.32–0.59; \( p < 0.001 \)) in patients at risk for acute renal impairment. However, the data for the use of this agent as prophylaxis for contrast-induced nephropathy have not been robust. After a starting dose of 0.1–0.3 \( \mu g/ \) kg/min, the fenoldopam dosage may be increased in increments of 0.05–0.1 \( \mu g/ \) kg/min every 15 minutes until the target BP is reached. The maximal infusion rate reported in clinical studies was 1.6 \( \mu g/ \) kg/min. There is limited information on the use of fenoldopam in patients age 65 years or older, although anecdotal experience has not identified differences in responses between the elderly and younger patients. In general, dosage selection for an elderly patient should be cautious, usually starting at the low end of the dosing range. The onset of action of i.v. fenoldopam is \(<5\) minutes, with a duration of 30 minutes. The half-life of the drug is 9.8 minutes. Common adverse events associated with fenoldopam include headache, flushing, tachycardia, dizziness, and a dose-related increase in intracocular pressure. Thus, fenoldopam should be administered with caution or avoided in patients with glaucoma. The drug preparation contains sodium metabisulfate and should be avoided in patients with a sulfite allergy.

**Enalaprilat.** Enalaprilat is an i.v. angiotensin-converting-enzyme (ACE) inhibitor that blocks the conversion of angiotensin I to angiotensin II, a potent vasoconstrictor. Its vasodilatory properties are due to the decreased production of angiotensin II. Bradykinin-induced vasodilation may also play a role, since ACE is responsible for bradykinin degradation, and bradykinin levels increase after administration of ACE inhibitors. In patients with hypertension, administration of ACE inhibitors is associated with a decrease in total peripheral resistance but with little change in heart rate, cardiac output, or pulmonary occlusion pressures. For hypertension, enalaprilat 1.25 mg is administered every 6 hours intravenously over a 5-minute period. A clinical response is usually seen within 15 minutes. Peak effects after the first dose may not occur for up to 4 hours after administration. The peak effects of the second and subsequent doses may exceed those of the first. The onset of enalaprilat occurs in 15–30 minutes, and its duration of action is 12–24 hours. In contrast to shorter-acting vasodilators for hypertensive emergency, the enalaprilat dosage is not easily adjusted. Once a bolus dose is given, a longer time is needed before the clinical effects are seen. If hypotension occurs, the long duration of action is not a favorable property. The degree of BP lowering associated with ACE inhibitors is related to the pretreatment concentration of angiotensin II and plasma renin activity. In general, ACE inhibitors are more effective in patients with high renin levels, although these patients may have drastic drops in BP and should be closely monitored after receiving i.v. enalaprilat. Enalaprilat should be avoided in patients with acute MI and in patients with bilateral renal artery stenosis. In addition, ACE inhibitors are contraindicated in pregnancy and should not be used to treat preeclampsia or eclampsia.

For patients on diuretic therapy, the recommended starting dose is 0.625 mg administered over 5 minutes. Clinical response is usually seen within 15 minutes, although peak response may not occur until four hours after administration. The 0.625-mg dose may be repeated after one hour if there is inadequate clinical response. Additional doses of 1.25 mg may be given at six-hour intervals. For patients with a creatinine clearance of \( \leq 30 \) mL/min (serum creatinine concentration of \( \geq 3 \) mg/dL), the starting dose should be 0.625 mg, which may be repeated after one hour if the clinical response is inadequate. Additional doses of 1.25 mg may be given at six-hour intervals.

**Nesiritide.** Nesiritide, a recombinant B-type natriuretic peptide, is a venous, an arterial, and a coronary vasodilator. It reduces preload and afterload, increases cardiac output without direct inotropic effects, improves echocardiographic indexes of diastolic function, and decreases dyspnea when used in the setting of decompensated congestive heart failure with APE. It is structurally identical to the peptide produced by cardiac ventricles in response to the increased wall stress, hypertrophy, and volume overload commonly seen in APE.

Nesiritide use is controversial at this time. One meta-analysis of pooled data from existing trials found that nesiritide may be associated with a statistically nonsignificant trend of mortality within the first month after its use for the treatment of decompensated congestive heart failure; however, the analysis was not based on an adequately powered prospective trial. Instead, data from pooled trials were analyzed, allowing the authors to qualify their results as hypothesis generating rather than as conclusive evidence of harm. A subsequent large, prospective, randomized trial investigated the adjunctive administration of nesiritide on an...
outpatient basis for advanced heart failure. A total of 300 patients received once-weekly infusions and 300 received twice-weekly infusions of nesiritide for three months; all were followed for an additional three months. Nesiritide was administered as a bolus dose of 2 μg/kg, followed by an infusion of 0.01 μg/kg/min for 4–6 hours. No effect on mortality was found. A study is currently recruiting patients to assess rehospitalization due to heart failure and all-cause mortality through day 30 and dyspnea symptoms at 6 and 24 hours after nesiritide initiation. Nesiritide infusions lasting longer than 24 hours appear to be associated with elevated markers of worsening renal function in patients with acute decompensated congestive heart failure.

For i.v. treatment of adult patients with acute decompensated congestive heart failure, nesiritide is given with acute decompensated congestive heart failure, nesiritide is administered once-weekly infusions and all-cause congestive heart failure.95 A total of 300 patients received once-weekly infusions and 300 received twice-weekly infusions of nesiritide for three months; all were followed for an additional three months. Nesiritide was administered as a bolus dose of 2 μg/kg, followed by an infusion of 0.01 μg/kg/min for 4–6 hours. No effect on mortality was found. A study is currently recruiting patients to assess rehospitalization due to heart failure and all-cause mortality through day 30 and dyspnea symptoms at 6 and 24 hours after nesiritide initiation. Nesiritide infusions lasting longer than 24 hours appear to be associated with elevated markers of worsening renal function in patients with acute decompensated congestive heart failure.

For i.v. treatment of adult patients with acute decompensated congestive heart failure, nesiritide is given as a 2-μg/kg bolus dose (over one minute), then a continuous infusion of 0.01 μg/kg/min.22 The medication is reconstituted, and the bolus dose withdrawn directly from the bag. Higher initial doses are not recommended. However, at 3-hour intervals, the dosage may be increased by 0.005 μg/kg/min after a bolus dose of 1.0 μg/kg, up to a maximum of 0.03 μg/kg/min.22 Its half-life is 18 minutes, it is metabolized predominately by endothelial receptors, and 60–70% of the drug’s effect is seen within 15 minutes.

Table 1 lists the agents for treating hypertensive emergencies with comorbidities.

Table 1. Agents for Treating Hypertensive Emergencies with Comorbidities

<table>
<thead>
<tr>
<th>Comorbidity</th>
<th>Preferred Agent(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute aortic dissection</td>
<td>Esmolol&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Acute congestive heart failure</td>
<td>Nesiritide,&lt;sup&gt;c&lt;/sup&gt; nitroglycerin, nitroprusside</td>
</tr>
<tr>
<td>Acute intracerebral hemorrhage</td>
<td>Labetalol, nicardipine</td>
</tr>
<tr>
<td>Acute ischemic stroke</td>
<td>Labetalol, nicardipine</td>
</tr>
<tr>
<td>Acute myocardial infarction</td>
<td>Clevidipine,&lt;sup&gt;d&lt;/sup&gt; esmolol, labetalol, nicardipine,&lt;sup&gt;e&lt;/sup&gt; nitroglycerin</td>
</tr>
<tr>
<td>Acute pulmonary edema</td>
<td>Nesiritide,&lt;sup&gt;f&lt;/sup&gt; nitroglycerin, nitroprusside</td>
</tr>
<tr>
<td>Acute renal failure</td>
<td>Clevidipine, fenoldopam, nicardipine</td>
</tr>
<tr>
<td>Eclampsia or preeclampsia</td>
<td>Hydralazine, labetalol, nicardipine</td>
</tr>
<tr>
<td>Perioperative hypertension</td>
<td>Clevidipine, esmolol, nicardipine, nitroglycerin, nitroprusside</td>
</tr>
<tr>
<td>Sympathetic crisis or catecholamine</td>
<td>Clevidipine, fenoldopam, nicardipine, toxicity phenolamine</td>
</tr>
</tbody>
</table>

<sup>a</sup>Agents listed in alphabetical order, not in order of preference.
<sup>b</sup>May be used in combination with a vasodilator like dihydropyridine calcium-channel blocker or nitroprusside; however, β-blockade must precede administration of these agents.
<sup>c</sup>Use is controversial.
<sup>d</sup>May be used in patients with heart rate of <70 beats/min.

References


References


Intravenous therapy