Drug Treatment for Hypertensive Emergencies

NEW CONCEPTS AND EMERGING TECHNOLOGIES FOR EMERGENCY PHYSICIANS

Dear Colleagues:

Hypertensive emergencies represent one of the most common presentations to the emergency department, as many as 3% of visits in one study. End organ damage which can include the brain, heart, aorta, kidneys, and eyes typically defines the condition with treatment specific for the organ involved. For emergency physicians, early diagnosis and appropriate treatment are essential for minimizing injury due to elevated blood pressure. In some cases, this management of hypertension can be life saving.

Drs. David Cline and Alpesh Amin provide, in this EMCREG-International Newsletter, an excellent guide to parenteral medications for hypertension. Based on an initial concise discussion of the epidemiology, pathophysiology, and clinical presentation of hypertensive emergencies, the authors focus on the specific agents for treating these conditions with appropriate therapeutic objectives and goals for the clinician. Provided in tabular form, this information can be readily obtained by busy emergency physicians and used to help in the care of patients with hypertension. It is our hope this EMCREG-International Newsletter will be useful to you in the diagnosis and treatment of patients with hypertensive emergencies.

Sincerely,

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Objectives:

1) Describe the major categories of hypertensive emergencies and the clinical findings of end-organ damage.
2) Define the first line parenteral treatment for each diagnostic category of hypertensive emergency.
3) Describe the mechanism of action for each of the recommended parenteral antihypertensive medications and the precautions associated with their administration.

Introduction

Hypertensive emergency is defined as an acute elevation of blood pressure associated with end organ damage, specifically, acute effects on the brain, heart, aorta, kidneys and/or eyes. Epidemiologic studies of this condition are hampered by the lack of diagnostic criteria existing to differentiate hypertensive emergency from less serious clinical presentations associated with hypertension, despite the need for such description. This Newsletter focuses on the drug treatment of hypertensive emergencies, primarily parenteral therapy. The drugs of choice for the treatment of each diagnostic category are discussed with the evidence supporting these recommendations.

Epidemiology

Acute hypertensive emergencies are found most commonly in patients with known hypertension who are non-compliant with antihypertensive therapy. Although reported to represent as many as 3% of ED visits in one study, more recent assessments rank hypertensive emergencies...
as representing between 0.5% and 0.6% of ED visits. It is estimated that 1% of patients with a history of hypertension will develop a hypertensive emergency. Categories of hypertensive emergencies are listed in Table 1. Not all patients with the listed disorders necessarily have elevated blood pressure. Clinicians should also be aware that in certain conditions, elevated blood pressures may be a better prognostic sign than hypotension, such as in the case of acute ischemic stroke.

**Pathophysiology**

The pathophysiology of hypertensive emergencies is poorly understood, but is known to vary in part by etiology. A recognized phenomenon is a sudden increase in systemic vascular resistance secondary to circulating humoral vasoconstrictors. There is also evidence of a critical arterial pressure being reached which overwhelms the target organ’s ability to compensate for the increased arterial pressure, limiting blood flow to the organ. These initial events trigger mechanical wall stress as well as endothelial injury leading to increased permeability, activation of the coagulation cascade as well as platelets, and deposition of fibrin. Ultimately fibrinoid necrosis of the arterioles ensues which potentially can be recognized clinically by hematuria when the kidney is involved, or arterial hemorrhages or exudates on fundus exam when the eye is involved. The renin-angiotensin system may be activated, leading to further vasoconstriction. Volume depletion may occur through pressure natriuresis, prompting further release of vasoconstrictors from the kidney. These combined effects produce hypoperfusion of the end organs with ischemia and dysfunction.

There is evidence the rate of blood pressure elevation is an important determinate of end organ injury. As the majority of patients who present with a hypertensive emergency have a history of hypertension (84-93%), it is important to understand the chronic effects of hypertension on cerebral blood flow. In normal individuals, changes in cerebral perfusion

<table>
<thead>
<tr>
<th>Table 1. Hypertensive Emergencies</th>
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<tbody>
<tr>
<td><strong>Diagnostic Category</strong></td>
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<tr>
<td>Acute aortic dissection</td>
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<tr>
<td>Acute pulmonary edema</td>
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<tr>
<td>Acute myocardial infarction</td>
</tr>
<tr>
<td>Acute coronary syndrome</td>
</tr>
<tr>
<td>Acute renal failure</td>
</tr>
<tr>
<td>Severe Pre-eclampsia, HELLP syndrome, eclampsia</td>
</tr>
<tr>
<td>Hypertensive encephalopathy</td>
</tr>
<tr>
<td>Subarachnoid hemorrhage</td>
</tr>
<tr>
<td>Intracranial hemorrhage</td>
</tr>
<tr>
<td>Acute ischemic stroke</td>
</tr>
<tr>
<td>Acute postoperative hypertension*</td>
</tr>
<tr>
<td>Sympathetic crisis*</td>
</tr>
</tbody>
</table>

Abbreviations: CT = computed tomography, HELLP = hemolysis, elevated liver enzymes, low platelets, MRI = magnetic resonance imaging.

*In this syndrome, acute end organ dysfunction may not be measurable, but complications affecting the brain, heart, or kidneys may occur in the absence of acute treatment.
pressure has little effect on cerebral blood flow over a wide range of arterial pressures.\textsuperscript{8} Hypertensive individuals have their cerebral autoregulation curves shifted to the right, and therefore, require higher arterial pressures to maintain cerebral blood flow.\textsuperscript{9,10} Both normotensive and hypertensive individuals lose autoregulatory ability when arterial pressures are reduced by 25\%, but the thresholds are different.

### Clinical Presentation

The clinical presentation and the initial blood pressures vary widely between the different causes of hypertensive emergencies as listed in Table 1. Acute aortic dissection is an important diagnosis to make as it is treated differently than other hypertensive emergencies. Patients present with abrupt, severe onset of pain (90\%), usually in the chest (78\%), typically described as tearing or ripping, and radiating to the inter-scapular region.\textsuperscript{11} Only 31\% have pulse deficits, based on blood pressure differentials, 28\% have a diastolic murmur, and 17\% have neurologic deficits. Chest radiograph is abnormal in 90\%, but the significance of this finding is frequently missed by the initial examining physician as the signs are multiple and not specific for aortic dissection such as abnormal aortic contour, pleural effusion, displaced intimal calcification, or wide mediastinum.\textsuperscript{11} Only 49\% of patients with aortic dissection have elevated blood pressure defined as over 140/90 mm Hg.\textsuperscript{12} Aortic dissection should be suspected in patients presenting with sudden onset of otherwise unexplained chest pain that radiates to the back, or in a patient with sudden onset of pain associated with any of the physical examination abnormalities described previously.

Patients presenting with chest pain should have an electrocardiogram and serum cardiac biomarkers depending on physician suspicion of acute coronary syndrome (ACS). Patients with severe hypertension and shortness of breath may have pulmonary edema, frequently with diastolic dysfunction.\textsuperscript{13} The onset of an acute severe mitral regurgitation murmur due to papillary muscle rupture is an important physical sign which may herald the need for emergency surgery. Patients with elevated blood pressure associated with sudden onset of headache, neurological deficit, or altered mental status should be suspected of having an intracranial etiology of a hypertensive emergency or hypertensive encephalopathy after the other forms of cerebral vascular disease are ruled out with appropriate testing. Patients with hypertensive encephalopathy will have altered mental status, frequently accompanied by headache, vomiting, and occasionally seizures. Some may have papilledema (34\%), retinal hemorrhages or exudates (25\%), or hematuria (60\%). Focal neurologic deficits are more commonly associated with stroke.

The diagnosis of hypertensive encephalopathy can be confirmed with the finding of cerebral edema on MRI, but treatment should not be withheld for confirmation.

Patients with new onset renal failure may have peripheral edema, oliguria, loss of appetite, nausea and vomiting, orthostatic changes, and or confusion. Renal function tests and urinalysis confirm the diagnosis. Patients with eclampsia present later in pregnancy with edema, and proteinuria, but may develop hemolysis, elevated liver enzymes, and a low platelet count. Patients with sympathetic crisis present with symptoms typical of the underlying mechanism. Patient with pheochromocytoma have headache, alternating periods of elevated blood pressure, tachycardia, and flushed skin intermingled with periods of normal blood pressure. Patients using recreational cocaine, amphetamines, or phenylcyclidine may present after inadvertent or purposeful overdose with tachycardia, diaphoresis, and hypertension, with or without mental status changes. A urine drug screen will most commonly yield positive results.

### Suggested Agents, Indications for Treatment

Table 2 lists the suggested agents for the management of hypertensive emergencies categorized by diagnosis. Therapeutic goals are listed for each diagnosis, with risks of therapy pertinent to each, and pearls of management. In general, the agent listed first is the preferred agent when one exists. Recommendations contained within the table are referenced when evidence from studies exists, or when guidelines have been published. Recommendations for a therapeutic goal in acute aortic dissection vary between SBP of <140 to <110 mm Hg.\textsuperscript{14,17} Aortic dissection provides an example of the paucity of randomized controlled studies to guide the treatment of hypertensive emergencies.\textsuperscript{18}
### Table 2. Suggested Agents for Acute Management of Hypertensive Crisis Stratified by Diagnosis

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Suggested Agents</th>
<th>Therapeutic Goal</th>
<th>Risk of Therapy</th>
<th>Pearls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute aortic dissection</td>
<td>- Labetalol&lt;sub&gt;10&lt;/sub&gt; IV continuous drip</td>
<td>- SBP 100-120 mm Hg, expert review and guideline&lt;sup&gt;10&lt;/sup&gt;</td>
<td>- Hypotension</td>
<td>- Avoid volume depletion</td>
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<tr>
<td></td>
<td>- Esmolol&lt;sub&gt;10&lt;/sub&gt; IV, bolus, then continuous drip</td>
<td>- Reduction of shear forces by reduction of BP and HR</td>
<td>- Nitroprusside requires continuous BP monitoring</td>
<td>- Always measure BP in both arms</td>
</tr>
<tr>
<td></td>
<td>- Nitroglycerin&lt;sub&gt;10&lt;/sub&gt; IV continuous drip (after β blocker)</td>
<td></td>
<td>- Respiratory distress in COPD/asthma patients; test dose of esmolol recommended; switch to diltiazem if esmolol intolerant&lt;sup&gt;11&lt;/sup&gt;</td>
<td>- Always use β-blocker prior to vasodilators; nitroprusside alone increases wall stress due to reflex tachycardia.</td>
</tr>
<tr>
<td></td>
<td>- Nitroglycerin&lt;sub&gt;10&lt;/sub&gt; sublingual, topical, or IV continuous drip&lt;sup&gt;12,13&lt;/sup&gt;</td>
<td></td>
<td></td>
<td>- IV nitrates dilate capacitance vessels at low doses, higher doses dilate arterioles and lower BP</td>
</tr>
<tr>
<td></td>
<td>- Enalapril&lt;sub&gt;12&lt;/sub&gt; IV</td>
<td>- Reduction of BP by 20-30%,&lt;sup&gt;13&lt;/sup&gt;</td>
<td>Hypotension (enalapril)</td>
<td>- Hypotension may occur with first dose of enalapril&lt;sup&gt;14&lt;/sup&gt;</td>
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<tr>
<td></td>
<td>- Furosemide IV (nitrates should be added to diuretics)&lt;sup&gt;13,14&lt;/sup&gt; continuous drip (after β blocker)</td>
<td></td>
<td>- Diuretics and ACE inhibitors can exacerbate renal dysfunction</td>
<td></td>
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<tr>
<td></td>
<td>- Nitroglycerin IV continuous drip</td>
<td>- Symptomatic relief</td>
<td>- Lower survival rates with diuretics alone&lt;sup&gt;14,15&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Acute pulmonary edema</td>
<td>- Nitroglycerin sublingual, topical, or IV continuous drip&lt;sup&gt;14&lt;/sup&gt;&lt;sup&gt;15&lt;/sup&gt;</td>
<td>- No more than 20-30% reduction for SBP &gt; 160 mm Hg&lt;sup&gt;15&lt;/sup&gt;</td>
<td>β blockade can exacerbate left ventricular failure</td>
<td>- Most hypertension will receive with time and benzodiazepines</td>
</tr>
<tr>
<td></td>
<td>- Nitroglycerin&lt;sub&gt;15&lt;/sub&gt; sublingual, topical, or IV continuous drip</td>
<td>- Reduction of ischemia</td>
<td>Blood pressures &gt; 185/100 mm Hg contraindicates thrombolytic use</td>
<td>- Watch respiratory rate</td>
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<tr>
<td></td>
<td>- β blocker, such as metoprolol&lt;sub&gt;15&lt;/sub&gt; or labetalol bolus therapy</td>
<td>- Spontaneous diuresis after vasodilation</td>
<td>- β blockade can cause alpha storm and increase cocaine toxicity</td>
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<tr>
<td></td>
<td>- Nitroglycerin&lt;sub&gt;15&lt;/sub&gt; sublingual, topical, or IV continuous drip</td>
<td>- Uneroposed β blockade can cause ischemic infarction and bleeding</td>
<td>Labetalol has been used in this setting but is not recommended&lt;sup&gt;16&lt;/sup&gt;</td>
<td></td>
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<tr>
<td></td>
<td>- Furosemide IV (nitrates should be added to diuretics)&lt;sup&gt;15&lt;/sup&gt; continuous drip (after β blocker)</td>
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<tr>
<td>Acute coronary syndrome</td>
<td>- Benzodiazepine&lt;sup&gt;16&lt;/sup&gt; IV bolus</td>
<td>- Reduction of excessive sympathetic drive</td>
<td>Hypotension</td>
<td>- Avoid ACE inhibitor acutely (some authors contradict this caution)&lt;sup&gt;17&lt;/sup&gt;</td>
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<tr>
<td></td>
<td>- Nitroglycerin&lt;sub&gt;16&lt;/sub&gt; IV bolus, then continuous drip</td>
<td>- Symptom relief</td>
<td>- IV bolus reduces mortality&lt;sup&gt;18&lt;/sup&gt;</td>
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<td></td>
<td>- Phentolamine&lt;sub&gt;16&lt;/sub&gt; IV bolus, then continuous drip</td>
<td></td>
<td>- Beware of hypotension with therapy; consider IV infarct and volume depletions</td>
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<tr>
<td></td>
<td>- Verapamil&lt;sub&gt;16&lt;/sub&gt; IV bolus, then continuous drip</td>
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<tr>
<td>Acute renal failure</td>
<td>- Labetalol&lt;sub&gt;17&lt;/sub&gt; bolus</td>
<td>- Reduction of BP by no more than 20% acutely&lt;sup&gt;17&lt;/sup&gt;</td>
<td>Hypotension</td>
<td>- Avoid nitroprusside</td>
</tr>
<tr>
<td></td>
<td>- Nicardipine&lt;sub&gt;17&lt;/sub&gt; IV continuous drip</td>
<td></td>
<td>- AV blockade can cause ischemic infarction</td>
<td>- Avoid ACE inhibitor acutely (some authors contradict this caution)&lt;sup&gt;17&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>- Fenoldopam&lt;sub&gt;17&lt;/sub&gt; IV continuous drip</td>
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<tr>
<td></td>
<td>- Diazaxi</td>
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<tr>
<td>Severe Pre-eclampsia, HELLP syndrome, eclampsia</td>
<td>- Labetalol&lt;sub&gt;18&lt;/sub&gt; bolus</td>
<td>- &lt;160/110 mm Hg&lt;sup&gt;18&lt;/sup&gt;</td>
<td>Hypotension</td>
<td>- Avoid nifedipine in patients over 45, or those with CAD</td>
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<td></td>
<td>- Nifedipine&lt;sub&gt;18&lt;/sub&gt; orally (nicardipine may be better tolerated)&lt;sup&gt;18&lt;/sup&gt;</td>
<td>- &lt;150/100 mm Hg if decreased platelets (≤100,000/mm&lt;sup&gt;3&lt;/sup&gt;)&lt;sup&gt;18&lt;/sup&gt;</td>
<td>- Hydralazine yields an unpredictable therapeutic response and therefore is not recommended&lt;sup&gt;19&lt;/sup&gt;</td>
<td>- Use MgSO&lt;sub&gt;4&lt;/sub&gt; to prevent seizures</td>
</tr>
<tr>
<td>Hypertensive encephalopathy</td>
<td>- Nicardipine&lt;sub&gt;19&lt;/sub&gt; IV continuous drip</td>
<td>- Decrease MAP 15-20%</td>
<td>Hypotension</td>
<td></td>
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<tr>
<td></td>
<td>- Labetalol&lt;sub&gt;19&lt;/sub&gt; IV continuous drip</td>
<td></td>
<td>More aggressive lowering may lead to ischemic infarction</td>
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<tr>
<td></td>
<td>- Fenoldopam&lt;sub&gt;19&lt;/sub&gt; IV continuous drip</td>
<td></td>
<td>Autoregulation of cerebral perfusion may be significantly impaired, therefore, avoid rapid BP manipulation</td>
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<tr>
<td>Subarachnoid hemorrhage</td>
<td>- Labetalol&lt;sub&gt;20,21&lt;/sub&gt; IV bolus, then continuous drip</td>
<td>- BP &lt; 160 mm Hg or MAP &lt; 130 mmHg to prevent rebleeding&lt;sup&gt;20&lt;/sup&gt;</td>
<td>Hypotension</td>
<td>- Avoid nifedipine in patients over 45, or those with CAD</td>
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<td></td>
<td>- Nicardipine&lt;sub&gt;20,21&lt;/sub&gt; IV continuous drip</td>
<td>- Some neurosurgeons may prefer therapeutic hypertension to treat vasospasm&lt;sup&gt;20&lt;/sup&gt;</td>
<td>- Early ICH growth often occurs in the first 6 hours. During this time, BP control may diminish growth</td>
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<td></td>
<td>- Esmolol&lt;sub&gt;20,21&lt;/sub&gt; IV, bolus, then continuous drip</td>
<td></td>
<td>- Avoid hypotension and monitor carefully to maintain SBP ≥ 120 to maintain cerebral perfusion</td>
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<td></td>
<td>- &lt;140/100 mm Hg to 130 mmHg to prevent rebleeding&lt;sup&gt;21&lt;/sup&gt;</td>
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<tr>
<td>Intracranial hemorrhage</td>
<td>- Labetalol&lt;sub&gt;22,23&lt;/sub&gt; IV bolus, or continuous drip</td>
<td>- For patients with any evidence of potential elevation of ICP, treat elevated BP to a target MAP of 130 mm Hg&lt;sup&gt;22&lt;/sup&gt;</td>
<td>Clinical and CT predictors of elevated ICP include: decreased LOC, evidence of midline shift, hematoma volume &gt; 30 ml</td>
<td>- Early ICH growth often occurs in the first six hours. During this time, BP control may diminish growth</td>
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<td>- Nicardipine&lt;sub&gt;22,23&lt;/sub&gt; IV continuous drip</td>
<td>- If there is no clinical suspicion of elevated ICP, treat to a MAP of 110, or SBP of 160 mm Hg&lt;sup&gt;23&lt;/sup&gt;</td>
<td>- Avoid precipitous drops in BP&lt;sup&gt;23&lt;/sup&gt;</td>
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<tr>
<td></td>
<td>- Esmolol&lt;sub&gt;22,23&lt;/sub&gt; IV, bolus, then continuous drip</td>
<td></td>
<td>- Elevate blood pressure commonly decreases over the first few hours after acute stroke without therapy</td>
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<tr>
<td>Acute ischemic stroke</td>
<td>- Labetalol&lt;sub&gt;24&lt;/sub&gt; IV bolus (start with 10 mg, or continuous drip)</td>
<td>- If fibrinolytic therapy planned, treat if &gt; 185/110 mm Hg</td>
<td>Lowering of blood pressure may significantly worsen ischemia and deficit</td>
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<td></td>
<td>- Nifedipine&lt;sub&gt;24&lt;/sub&gt; paste 1-2 inches</td>
<td>- Treat if &gt; 220/120 mm Hg on third measurement, spaced 15 minutes apart&lt;sup&gt;24&lt;/sup&gt;</td>
<td>- Avoid lowering blood pressure more than 10-15% in first 24 hours</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Nicardipine&lt;sub&gt;24&lt;/sub&gt; IV continuous drip</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Acute postoperative hypertension</td>
<td>- Nicardipine&lt;sub&gt;24&lt;/sub&gt; IV continuous drip</td>
<td>- Consider pre-operative BP for threshold to treat, but mild elevation is acceptable&lt;sup&gt;24&lt;/sup&gt;</td>
<td>Hypotension</td>
<td></td>
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<tr>
<td></td>
<td>- Labetalol&lt;sub&gt;24&lt;/sub&gt; IV bolus, or continuous drip</td>
<td>- Consider immediate surgical site complications such as bleeding&lt;sup&gt;24&lt;/sup&gt;</td>
<td>- Ensure that pain, anxiety, and temperature are controlled&lt;sup&gt;24,25&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Esmolol&lt;sub&gt;24&lt;/sub&gt; IV, bolus, then continuous drip</td>
<td>- &lt;180/110 mmHg/g is a general guideline</td>
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</table>

Abbreviations: ACE = angiotensin converting enzyme, BP = blood pressure, CAD = coronary artery disease, CT = computed tomography, HR = heart rate, IV = intravenous, MAP = mean arterial pressure, SAH = subarachnoid hemorrhage, SBP = systolic blood pressure
The value of nitrates in acute decompensated heart failure has been demonstrated by observation data, and two randomized trials. Diuretics when used alone in the treatment of decompensated heart failure, without vasodilators, have been associated with lower survival rates. The priority in the treatment of ACS is reversing ischemia, however, two mainstays of therapy, nitroglycerin and beta-blockers, also reduce blood pressure. In patients with systolic dysfunction, nicardipine has a favorable effect on coronary blood flow, however this group less commonly presents with marked hypertension.

The treatment of acute sympathetic crisis, in the case of cocaine or amphetamine abuse, deserves special consideration. The preferred initial treatment of this combined toxicologic and hypertensive emergency is benzodiazepines, such as lorazepam or diazepam, in repeated intravenous doses. The patient should be monitored for symptomatic fall in respiratory rate associated with marked sedation. If first line treatment is not successful, nitroglycerin, phentolamine, or calcium channel blocking agents may be used. Beta blockers are not recommended because beta receptor blockade can cause unopposed alpha storm and increase cocaine toxicity. Labetalol has been used in this setting due to its dual alpha and beta blocking effects, however, it is not recommended as it is a weak alpha blocking agent compared to its beta effects with a ratio of 1:7.

In the treatment of eclampsia, labetalol has been tested in several trials and is the preferred agent. Nifedipine, an agent discouraged in other settings, has performed favorably in the setting of pre-eclampsia without significant side effects. Hydralazine formerly was considered the drug of choice, but is no longer recommended due to its unpredictable therapeutic profile. ACE inhibitors are contraindicated in pregnancy due to their teratogenic effects on the fetus. The treatment goal for pre-eclampsia is lowered, from a goal of < 160/110, to <150/100 mm Hg, in the presence of a low platelet count, defined in this setting as less than 100,000 mm³.

Blood pressure reduction in the setting of neurologic emergencies typically requires emergency computer tomographic (CT) scanning to determine diagnosis, treatment thresholds, and priorities. Hypertensive encephalopathy is the clearest indication for blood pressure reduction but vascular disorders including ischemic stroke must be ruled out first. This requires astute clinical judgment to differentiate between these two clinical diagnoses (see Clinical Presentation above). Blood pressure reduction is controversial in the setting of acute vascular lesions, subarachnoid hemorrhage (SAH), intracranial hemorrhage, and ischemic stroke. Untreated vascular spasm in the setting of subarachnoid hemorrhage is associated with deterioration, and has been successfully treated with oral nimodipine, a calcium channel blocker that is not given to reduce blood pressure, but may affect pressures. When the decision to lower blood pressure is made for SAH patients, the purpose is to prevent rebleeding, which has been associated with blood pressures above 160/100 mm Hg. Other treatment measures are advocated to treat vasospasm, including therapeutic hypertension with vasopressors. This is controversial but still advocated as some medical centers. Therefore, clinicians should be familiar with the protocols of their own institutions prior to treating blood pressure.

Recent guidelines for the treatment of both hemorrhagic and ischemic stroke have cautioned clinicians concerning the paucity of evidence that treatment of blood pressure improves the course of stroke. These guidelines advocated prior recommendations for the control of blood pressure pending the results of several randomized controlled trials which should determine optimal care.

Treatment of acute post-operative hypertension (APH) is an issue which is increasingly being managed by non-anesthesiologists with the use of out-patient surgical centers. Beginning within 2 hours of surgery, APH resolves by six hours post surgery. It is more common with vascular procedures, and is associated with serious neurologic, cardiovascular and surgical site complications. Despite long standing discussion of the disorder and the need for its management, no well accepted definition or treatment thresholds exist. Nicardipine, labetalol, esmolol, and a new investigational, ultrashort acting calcium channel blocker, clevidipine, have been shown to be effective in APH.

Pain and anxiety should be controlled prior to, or in concert with blood pressure reduction as needed.

**Pharmacologic Agents**

Parenteral agents used for hypertensive emergencies are listed in Table 3, including dosage, mechanisms, and warnings. Refer to Table 2 for indications. Other considerations for drug choice include ability to monitor the patient and comorbidities, including respiratory and vascular disease.

**Beta-Blockers**

Labetalol is the most commonly used parenteral antihypertensive agent in the emergency department. Labetalol is unique among commonly used β-blockers as it also has selective α-1 inhibitory effects, although its α-1 effects are significantly less than its non-selective β-blocking effects by seven fold. It has broad application for hypertensive emergencies with the exception of...
### Table 3. Parenteral Agents Used for Hypertensive Emergencies

<table>
<thead>
<tr>
<th>DRUG</th>
<th>DOSAGE</th>
<th>MECHANISM/COMMENTS</th>
<th>WARNINGS</th>
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<tbody>
<tr>
<td>Labetalol</td>
<td><strong>Bolus:</strong> 20 mg (0.25 mg/kg for an 80-kg patient) IV over 2 min; may administer 40-80 mg at 10-min intervals, up to 300 mg total dose. <strong>Continuous infusion:</strong> Initially, 2 mg/min; titrate to response up to 300 mg total dose, if needed.</td>
<td>Combined selective α-1 adrenergic and nonselective β-adrenergic receptor blocker with an α- to β-blocking ratio of 1:7. Effect in 2-5 min, peaking by 15 min, duration 2-4 hr. Renal, cerebral, coronary blood flow maintained, minimal placental transfer.</td>
<td>Avoid use in patients with bradycardia; heart block; uncompensated cardiac failure, active bronchospasm; patients receiving IV verapamil or diltiazem. Caution in patients with liver impairment; bronchial asthma or COPD; elderly have less predictable response and more toxicity.</td>
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<tr>
<td>Esmolol</td>
<td><strong>Loading dose:</strong> 250-500 mcg/kg infused over 1-3 min IV, follow with <strong>Maintenance infusion:</strong> 50 mcg/kg/min IV over 4 min; if adequate effect not observed, repeat loading dose and increase infusion rate using increments of 50 mcg/kg/min IV for 4 min. This regimen can be repeated X 4 bolus doses and to an infusion rate of 200 mcg/kg/min.</td>
<td>Ultrashort acting, cardioselective, β-adrenergic receptor blocker. Onset within 60 seconds, duration 10-20 minutes. Ideal for use in patients at risk for complications from beta-blockers, especially patients with mild to moderately severe LV dysfunction or peripheral vascular disease. Half-life of 8 min, easily stopped.</td>
<td>Avoid use in patients: with bradycardia; heart block; cardiogenic shock; decompensated cardiac failure, active bronchospasm; patients receiving IV verapamil or diltiazem. Caution in patients with bronchial asthma, COPD; uncompensated cardiac failure; extravasation can lead to skin necrosis and sloughing.</td>
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<tr>
<td>Nicardipine</td>
<td><strong>Continuous infusion:</strong> start at a rate of 5 mg/hr. If target blood pressure not achieved in 15 minutes, increase dose by 2.5 mg/hr every 15 min until target pressure or the maximum dose of 15 mg/hr is reached.</td>
<td>Second generation dihydropyridine calcium channel blocker with vascular selectivity for the cerebral and coronary arteries. Onset of action is 3-10 min, duration is 1-4 hr.</td>
<td>Caution in decompensated heart failure. Avoid in patients receiving IV beta-blockers. Common side effects are headache, hypotension, vomiting, and tachycardia.</td>
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<tr>
<td>Nitroglycerin</td>
<td><strong>Sublingual</strong> 0.4 mg paste 1-2 inches. <strong>Continuous infusion:</strong> Start 5 mcg/min, increase by 5 mcg/min every 3-5 min to 20 mcg/min; if no response at 20 mcg/min, increase by 10 mcg/min every 3-5 min, up to 200 mcg/min (Note: many clinicians initiate with a higher infusion rate)</td>
<td>Potent venodilator and only at high doses affects arterial tone. Onset begins at 2 min, duration is 1 hour (pastes duration 3-4 hr, unless removed). Reduces blood pressure by reducing preload and cardiac output. Decreases coronary vasospasm and cardiac workload.</td>
<td>Avoid in cases of compromised cerebral and renal perfusion, concurrent use with phosphodiesterase-5 (PDE-5) inhibitors for erectile dysfunction (sildenafil, tadalafl, or vardenafil). Caution may cause hypotension with reflex tachycardia which is exacerbated by volume depletion as well as when given to patients using erectile dysfunction drugs.</td>
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<tr>
<td>Nitroprusside</td>
<td><strong>Continuous infusion:</strong> 0.3-0.5 mcg/kg/min IV initial infusion, increase in increments of 0.5 mcg/kg/min; titrate to desired effect. Rates &gt; 2 mcg/kg/min may lead to cyanide toxicity. Use lowest possible dose.</td>
<td>Arterial and venous vasodilator due to its interaction with oxyhemoglobin to produce nitric oxide. It decreases preload and afterload. Onset of action is in seconds, duration is 1-2 min. Cerebral blood flow is decreased while intracranial pressure is increased.</td>
<td>Avoid in patients with kidney or hepatic failure, or increased intracranial pressure. Caution: Intra-arterial monitoring is recommended; must be protected from light. Nitroprusside is recommended only when other agents fail. Coronary steal syndrome may occur.</td>
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<tr>
<td>Phentolamine</td>
<td><strong>Bolus load</strong> 5-20 mg IV every 5 min. <strong>Continuous infusion:</strong> 0.2-0.5 mcg/min.</td>
<td>α-1- and α-2-adrenergic blocking agent, effective for phaeochromocytoma and hypertensive laminergic-induced hypertension such as with cocaine intoxication.</td>
<td>Myocardial infarction, cerebrovascular spasm, and cerebrovascular occlusion have occurred following administration.</td>
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<td>Fenoldopam</td>
<td><strong>Continuous infusion:</strong> Start 0.1 mcg/kg/min, titrate to desired effect every 15 minutes, range 0.1 to 1.6 mcg/kg/min.</td>
<td>Dopamine-1 receptor agonist. Onset of action in 5 min, peak effect at 15 min, duration 30-60 min. Metabolized by liver, without P-450 system. Improves creatinine clearance, urine flow, and sodium excretion.</td>
<td>Caution: causes reflex tachycardia at higher doses. Concurrent acetaminophen may increase fenoldopam levels. May cause flushing, dizziness, vomiting.</td>
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<tr>
<td>Enalaprilat</td>
<td><strong>Bolus:</strong> 1.25 mg over 5 min every 4 to 6 hr, titrate at 12-24 intervals to a maximum of 5 mg every 6 hr.</td>
<td>Angiotensin converting enzyme inhibitor. Test dose of 0.625 mg recommended when concern for first dose hypotension exists.</td>
<td>Avoid: in pregnancy as it has been linked to fetal defects. Caution: First dose hypotension is common, especially in high renin states, may cause dizziness and headache.</td>
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cocaine intoxication and systolic dysfunction associated with decompensated heart failure. In these cases nicardipine may be a better choice when nitroglycerin fails. Metoprolol is indicated in acute coronary syndromes: give 5 mg IV every 5-15 minutes up to 15 mg. The short duration of esmolol provides a safety advantage in patients at risk for the adverse effects of β-blockers.

Calcium Channel Blockers

Clevidipine is third generation dihydropyridine CCB with ultrashort acting selective arteriolar vasodilator properties. It has been studied in the setting of cardiac surgery and is being developed for the treatment of hypertensive emergencies in the emergency department due to its ability to be titrated having a half life less than a minute. The Velocity Trial demonstrating efficacy in the emergency setting is currently pending publication. Nicardipine has a onset of action of 5-10 minutes, and can be titrated at 15 minute intervals. It has been found to be safe and effective in neurologic hypertensive emergencies as well as other conditions, and has a favorable effect on myocardial oxygen balance increasing both stroke index and coronary blood flow. Nifedipine use (10 mg orally) is discouraged in hypertensive emergencies, except in patients with pre-eclampsia.

Vasodilators

Until recently, nitroprusside has been the most commonly used drug for hypertensive emergencies because of rapid onset and its almost universal efficiency. However, its use has been decreasing because of awareness of its toxicity and the need for invasive monitoring. It remains the agent that should be considered when other agents fail, and can be added to other agents, such as esmolol, allowing for a lower less toxic dose. Nitroglycerin is weak arterial dilator (requiring high doses), but is recommended as a first line agent in the treatment of heart failure and acute coronary syndromes due to its favorable effects on coronary blood flow and cardiac workload. Its hypotensive effects are due to its reduction of preload and cardiac output, making it a poor choice in other hypertensive emergencies.

Other Agents

Clonidine has a unique role in hypertensive emergencies for the patient who recently stopped taking the drug, inducing a rebound hypertension. It can be given orally 0.2 mg in this setting, or a clonidine patch can be used for patients unable to take oral medications. Its effects begin at 30 to 60 minutes, and peak effects are seen at 2 to 4 hours. Fenoldopam is a unique peripheral dopamine receptor agonist, and has application in renal and neurologic related hypertensive emergencies. Phentolamine has been used successfully in cocaine related hypertensive emergencies. Enalaprilat, the only available intravenous ACE inhibitor, has special application in patients with heart failure or ACS, but caution should be exercised because of common first dose hypotension. A 0.625 mg test dose is recommended when this is a concern. Administration of enalaprilat also has been recommended as diagnostic maneuver to determine the contribution of high renin to the patient's blood pressure. Patients who respond are likely to have elevated renin.

Summary

Effective management of hypertensive emergencies requires careful consideration of the etiology and indicated treatment. Identification of aortic dissection and differentiating neurologic hypertensive emergencies are especially important to management decisions. This monograph describes the preferred treatments for each diagnostic category with currently available information. Further study may better determine the ideal agents for each clinical situation.

REFERENCES

Drug Treatment for Hypertensive Emergencies


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CME Post Test

After you have read the monograph carefully, record your answers by circling the appropriate letter answer for each question.

1. Which of the following drugs can be expected to have its hypotensive effect in less than two minutes:
   a. Intravenous labetalol, 20 mg
   b. Intravenous esmolol, loading dose of 500 mcg/kg
   c. Intravenous nicardipine, initiated at 5 mg/hour
   d. Intravenous enalaprilat, 1.25 mg

2. Which of the following drugs is contraindicated for the management of severe hypertension associated with cocaine overdose:
   a. Intravenous esmolol, loading dose of 500 mcg/kg
   b. Intravenous lorazepam, 2 mg
   c. Intravenous phentolamine, 5 mg
   d. Nitroglycerin, 0.4 mg, sublingual

3. Which of the following drugs should not be given as the first antihypertensive agent to a patient with aortic dissection:
   a. Intravenous labetalol, 20 mg
   b. Intravenous esmolol, loading dose of 500 mcg/kg IV
   c. Intravenous drip nitroprusside, 0.3 mcg/kg/min
   d. Intravenous metoprolol, 5 mg

4. Which of the following patients should not receive enalaprilat as part of their management:
   a. Patient with non-ST elevation myocardial infarction
   b. Patient with heart failure
   c. Patient with elevated renin
   d. Patient with pre-eclampsia

5. Which of the following are known effects of nitroprusside infusion:
   a. Production of alpha storm when given with a beta-blocker
   b. Release of cyanide (harmful) and production of nitric oxide (therapeutic effect)
   c. Idiosyncratic irreversible hypotension at initial infusion
   d. Metabolic alkalosis on prolonged infusion.

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