Hypertensive Emergencies and Urgencies: A Clinical Guide

K Subba Reddy

ABSTRACT
Hypertension being a common medical condition is resulting in increased hospital admissions worldwide and, moreover, hypertensive emergencies and urgencies have led to an increment in critical care patients. It is, therefore, evident that urgent diagnosis and immediate and appropriate treatment of these conditions is paramount in reducing mortality and morbidity.

Manifestations of the hypertensive emergencies and urgencies may vary depending on the target organ that is affected. Fortunately, more effective and relatively safe drugs are available, nowadays, to lower blood pressure (BP) quickly in these life-threatening situations. Critical care physicians should be familiar with all pharmacological and clinical actions of the medications available in treating these hypertensive emergencies, along with the appropriateness of the choice of medication in any given situation.

The purpose of review is to understand the therapeutic interventions in treating a hypertensive crisis.

Keywords: Acute aortic dissection, Hypertensive encephalopathy, Left ventricular failure, Pharmacological therapy.

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INTRODUCTION
Systemic hypertension is a common medical condition affecting over 1 billion people in the world. Hypertensive emergencies occur in up to 2% of patients with systemic hypertension. Early recognition, evaluation and appropriate treatment are important in the management of hypertensive urgencies and emergencies to prevent excessive morbidity. In some clinical circumstances, immediate reduction of blood pressure (BP) is indicated, not because of its absolute level but because of coexisting complications (e.g. aortic dissection, renal failure and acute left ventricular failure) which may make any degree of hypertension dangerous.

DEFINITION
The classification and approach to clinical hypertension have been reviewed by the Joint National Committee (JNC). Hypertensive crisis are, by convention, divided into emergencies and urgencies (Tables 1 and 2). Severe elevation of blood pressure (BP) in the presence of acute end organ damage leads to hypertensive emergency, whereas hypertensive urgencies occur without acute end organ damage. Distinguishing hypertensive urgencies from emergencies is critical in formulating the treatment plan. Patient with hypertensive urgency should have their BP reduced within 24 to 48 hours, whereas patients with hypertensive emergency should have their BP lowered immediately, but not to normal levels. The term ‘malignant hypertension’ has been used to describe a syndrome characterized by elevated BP accompanied by encephalopathy or acute nephropathy. This term, however, has been removed from national and international BP control guidelines and is best referred to as ‘hypertensive crisis’.

PATHOPHYSIOLOGICAL FACTORS
Hypertensive crisis is thought to be initiated by an abrupt increase in systemic vascular resistance likely related to neurohumoral activation. The subsequent increase in BP generates mechanical stress and endothelial injury leading to increased vascular permeability, activation of coagulation cascade and deposition of fibrin resulting in vaso-occlusion.

Patients with a hypertensive crisis frequently have thrombotic microangiopathy with severe microvascular abnormalities resulting in renal or cerebral dysfunction. Vanden born et al demonstrated increased levels of

<table>
<thead>
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<th>Table 1: Certain examples of hypertensive urgencies</th>
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<tr>
<td>Severe uncontrolled (asymptomatic) hypertension</td>
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<tr>
<td>Hypertension associated with burns</td>
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<tr>
<td>Perioperative hypertension</td>
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<tr>
<td>Uncontrolled hypertension in organ transplant patients</td>
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<td>Accelerated hypertension</td>
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<td>Severe hypertension in patients with coronary artery disease</td>
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<table>
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<th>Table 2: Certain examples of hypertensive emergencies</th>
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<td>Hypertensive encephalopathy</td>
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<tr>
<td>Malignant hypertension</td>
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<td>Acute pulmonary edema</td>
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<tr>
<td>Acute stroke (hemorrhagic)</td>
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<tr>
<td>Sympathetic excess syndromes</td>
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<tr>
<td>Eclampsia</td>
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<tr>
<td>Pheochromocytoma crisis</td>
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</table>
von Willebrand factor (VWF), VWF polypeptides, pro-
thrombin fragment 1 (F1R2) and plasmin-antiplasmin com-
plexes with reduced levels of ADAMTS13 in patients with
a hypertensive crisis when compared with normotensive
controls. Recent data suggest that endothelial dysfunction
may persist for years after the onset and resolution of a
hypertensive emergency.5,6

Some examples of hypertensive emergencies are
hypertensive encephalopathy, acute left ventricular
failure, acute aortic dissection, intracranial hemorrhage,
pheochromocytoma crisis, eclampsia and substance/
drug-induced acute hypertension. Some examples for
hypertensive urgencies are accelerated hypertension,
severe hypertension associated with organ transplant
patient, hypertension associated with burns, perioperative
hypertension and severe uncontrolled hypertension.

Selected Clinical Conditions

Acute Aortic Dissection

Aortic dissection should be considered in patients pre-
senting to the emergency department with acute chest
or abdominal pain and elevated BP (Table 3). There are
subtle differences between the pain caused due to aortic
dissection and that of myocardial infarction. However,
the pain due to dissection is abrupt in onset and is quite
severe immediately, whereas patients with myocardial
infarction often report a more insidious onset. Left
untreated, approximately three-fourth of the patients
with type A dissection (ascending aorta) die within
2 weeks of acute episodes, but with successful treatment
5 years survival rate is 75%.10 If the patient is hypertensive,
BP should be reversed to near normal levels with a drug
that causes the BP to come down smoothly rather that
dramatically. Direct venodilatation that reflexly stimulates
the heart rate are contraindicated in aortic dissection.10,11

Hypertensive Encephalopathy

Hypertensive encephalopathy is an uncommon deadly
complication of severe hypertension. Although encephalo-
pathy occurs mainly in patients with chronic uncontrolled
or malignant hypertension, it can also complicate sudden
hypertension of short duration. Hypertensive encephalo-
pathy 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 1 to 2 days to evolve.

Severe headache is a prominent symptom. Symptoms,
such as confusion and stupor, may appear simultaneous
or following the onset of headache. Other clinical features
may include vomiting and visual disturbances. On phys-
ical examination, the BP is invariably elevated but there
is no fixed level of BP above which encephalopathy is
likely to occur. The fundi reveal generalized arteriolar
spasm with exudates/hemorrhages. Papilledema is
present in most patients of encephalopathy.

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

Once hypertensive encephalopathy is diagnosed,
the BP should be lowered quickly, yet the diastolic BP
should probably remain at or slightly above 100 mm Hg.
Rapid treatment of severe hypertension produces prompt,
dramatic and significant relief of symptoms of hyper-
tensive encephalopathy. The goal of therapy is to prevent
permanent neurologic damage. In this regard, continuous
BP monitoring is often very useful.

Cerebrovascular Accidents

Most of the patients with cerebral ischemia present with
high BP regardless of subtype of infarct or pre-existing
hypertension. The elevated BP may be a protective
physiologic response to maintain cerebral perfusion
pressure in the ischemic area.9 The American stroke
association and European stroke guidelines recommend
treating hypertension if systolic BP is more than 220 mm Hg
or diastolic BP is more than 120 mm Hg in patients who are
not undergoing thrombolytic therapy for acute ischemic
strokes but BP control in patients due for thrombolytic
therapy is different, i.e. to maintain systolic BP < 185
mm Hg or diastolic BP < 110 mm Hg. For intracranial
hemorrhage patients presenting with systolic BP 150 to
220 mm Hg and without contraindication for acute lowering
of BP target, lowering the systolic BP to 140 mm Hg is safe
and can be useful for improving functional outcomes.

Pheochromocytoma Crisis

Blood pressure is markedly elevated during paroxysm
and patient may have profound sweating, marked
tachycardia, pallor, numbness, tingling and coldness of
the feet and hands. If pheochromocytoma is suspected,
alpha adrenergic blocking drug phentolamine should be

<table>
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<th>Table 3: Clinical manifestations of acute aortic dissection</th>
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<tbody>
<tr>
<td>Severe pain in the chest, neck or abdomen</td>
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<tr>
<td>Syncope</td>
</tr>
<tr>
<td>Sudden visual impairment</td>
</tr>
<tr>
<td>Dyspnea</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
</tr>
<tr>
<td>Melena/GI-GU blood loss</td>
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given in a dose of 1 to 5 mg intravenously, and repeated in few minutes if needed. A beta blocking drug may be useful if the patient has concomitant cardiac arrhythmia. A combined alpha and beta blocker like labetalol can also be used.12

**Sympathetic Crisis**

Most commonly seen are related to the use of drugs, such as amphetamines, cocaine and phencyclidine. Rarely, these crises may be seen with pheochromocytoma, patients receiving a monoamine oxidase inhibitor who ingest tyramine containing food, or patients who suddenly stop antihypertensive medications, such as clonidine or beta adrenergic antagonists. For hypertension associated with cocaine use, treat with benzodiazepines and avoid beta blocker therapy.14

**Eclampsia**

Hypertension is one of the most common medical disorders affecting pregnancy. Even though delivery of the fetus is the definitive treatment for pre-eclampsia and eclampsia, therapies like volume expansion, magnesium sulphate for seizure prophylaxis and hypertension control are pivotal. Loading dose of ~4 gm iv, followed by a constant infusion of 1 to 2 gm/hour. American college of obstetricians and gynecologists recommends keeping systolic BP between 140 and 160 mm Hg and diastolic BP between 90 and 105 mm Hg. Pre-eclampsia and eclampsia patients may have very labile BP, hence, it is better to monitor their BP more closely.

Hydralazine has been recommended as a drug of choice to treat severe pre-eclampsia and eclampsia. However, hydralazine has a number of properties that make it unsuitable for this indication. Its side effects are common and mimic symptoms of worsening pre-eclampsia. This drug can cause precipitous fall in BP compromising maternal cerebral perfusion pressure and uteroplacental blood flow. Angiotensin-converting-enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) should be avoided because of fetal or placental toxicity. Diuretics are avoided because of the volume-depleted state in pre-eclampsia.15

**Acute Pulmonary Edema (Left Ventricular Failure)**

Severe hypertension may cause acute left ventricular failure. Higher the BP, harder the left ventricle must work. Decreasing the work load of the failing myocardium should improve cardiac functions. In acute pulmonary edema, myocardial oxygen demand increases because of increased end diastolic fiber length and high left ventricular volume. Nitroglycerin sublingual or intravenous (IV) continuous drip, enlaprilat IV and frusemide IV are the agents generally used in treating hypertension with acute pulmonary edema.7,8

**Pharmacologic Agents used in the Treatment of Hypertensive Emergencies**

The pharmacologic agents used in the treatment of hypertensive emergencies are discussed in Table 4.

### Table 4: Parenteral drug options of hypertensive emergencies

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Administration</th>
<th>Onset of action</th>
<th>Duration of action</th>
<th>Adverse effects</th>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Labetalol</td>
<td>20–80 mg IV bolus every 10 mins; 2 mg/min infusion</td>
<td>IV bolus/infusion</td>
<td>5 minutes</td>
<td>3–6 hours</td>
<td>Nausea, vomiting, bronchospasm, heart block, orthostatic hypotension</td>
<td>Most hypertensive emergencies except heart failure</td>
</tr>
<tr>
<td>Sodium nitroprusside</td>
<td>0.25–10 μg/kg/min; maximal dose is ≤10 minutes</td>
<td>IV infusion</td>
<td>≤30 seconds</td>
<td>1–2 minutes</td>
<td>Hypotension, nausea, vomiting, muscle twitching, thiocyanate and cyanide intoxication, methemoglobinemia</td>
<td>Most hypertensive emergencies; caution with renal and hepatic insufficiency and high intracranial pressure</td>
</tr>
<tr>
<td>Hydralazine</td>
<td>10–20 mg IV; 10–50 mg IM</td>
<td>IV infusion/IM injection</td>
<td>10–20 minutes</td>
<td>4–12 hours</td>
<td>Reflex tachycardia, headache, nausea, vomiting, aggravation of angina</td>
<td>Eclampsia; caution with high intracranial pressure</td>
</tr>
<tr>
<td>Nitroglycerin</td>
<td>5–100 μg/min</td>
<td>IV infusion</td>
<td>2–5 minutes</td>
<td>3–5 minutes</td>
<td>Headache, nausea, vomiting, tolerance with prolonged use</td>
<td>Coronary insufficiency</td>
</tr>
<tr>
<td>Enalaprilat</td>
<td>1.25–5 mg every 6 hours</td>
<td>IV infusion</td>
<td>10–15 minutes</td>
<td>6–24 hours</td>
<td>Hypotension, renal failure</td>
<td>Acute left ventricular failure</td>
</tr>
<tr>
<td>Esmolol</td>
<td>50–200 mcg/kg/min</td>
<td>IV infusion</td>
<td>Rapid &lt; 1 minute</td>
<td>10–12 minutes</td>
<td>Hypotension, bradycardia, faintness, blurred vision</td>
<td>Severe hypertension in patients with tachycardia, coronary syndromes, and perioperative hypertension</td>
</tr>
</tbody>
</table>
**Labetalol**

Labetalol is a combined selective alpha adrenergic and beta adrenergic receptor blocker with an alpha to beta blocking ratio of 1:7. Labetalol is metabolized by the liver to form an inactive glucuronide conjugate. The hypotensive effect of labetalol begins within 2 to 5 minutes after its IV administration, reaching a peak at 5 to 15 minutes following administration, and lasting for about 2 to 4 hours. Due to its beta-blocking effects, the heart rate is either maintained or slightly reduced. Unlike pure beta adrenergic blocking agents that decrease cardiac output, labetalol maintains cardiac output. Labetalol reduces the systemic vascular resistance without reducing total peripheral blood flow. In addition, the cerebral, renal, and coronary blood flows are maintained. This agent has been used in the setting of pregnancy-induced hypertensive crisis, because little placental transfer occurs mainly due to the negligible lipid solubility of the drug. Labetalol may be administered as loading dose of 20 mg, followed by repeated incremental doses of 20 to 80 mg at 10 minutes intervals until the desired BP is achieved. Alternatively, after the initial loading dose, an infusion commencing at 1 to 2 mg/min and titrated up to until the desired hypotensive effect is achieved. Bolus injections of 1 to 2 mg/kg have been reported to produce precipitous falls in BP and should, therefore, be avoided. 

**Esmolol**

Esmolol is an ultrashort acting cardioselective beta adrenergic blocking agent. The onset of action is within 60 seconds, with duration of action of 10 to 20 minutes. The metabolism of esmolol is via rapid hydrolysis of ester linkages by red blood cell (RBC) esterases and is not dependent on renal or hepatic function. Due to its pharmacokinetic properties, some authors consider it an ‘ideal adrenergic blocker’ for use in critically ill patients. This agent is available for IV use both as a bolus and as an infusion. Esmolol is particularly useful in severe postoperative hypertension. Esmolol is a suitable agent in situations in which cardiac output, heart rate and BP are increased, and is administered as a 0.5 to 1 mg/kg loading dose over 1 minute, followed by an infusion starting at 50 mcg/kg/minutes and increasing up to 300 mcg/kg/min as necessary.

**Calcium Channel Blockers**

Clevidipine is third generation experimental 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 an onset of action of 5 to 10 minutes, and can be titrated at 15 minutes 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 possibly in patients with severe pre-eclampsia.

**Direct 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 a 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 a 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 a role in renal and neurologic related hypertensive emergencies. Phentolamine has been used successfully in cocaine related hypertensive emergencies and pheochromocytoma. Enalaprilat, the only available IV ACE inhibitor, has special application in patients with heart failure or acute coronary syndrome, but caution should be exercised because of common first dose hypotension. Administration of enalaprilat also has been recommended as a diagnostic maneuver to determine the contribution of high renin to the patient’s BP.
CONCLUSION

A fundamental therapeutic goal in the management of hypertensive emergencies/urgencies is to attain a safe level of BP quickly while minimizing the risk of unwanted hypotension. Most patients with uncontrolled hypertension are either noncompliant to therapy or have previously undiagnosed hypertension. Severe hypertension is associated with significant morbidity and, therefore, should be treated promptly. Long-term prognosis of patients with severe hypertension depends on good control of hypertension.

An important clinical decision is whether the patient’s degree of hypertension requires immediate reduction of BP and hospital care. The choice of parenteral or oral antihypertensive drugs depends on the clinical evaluation, available laboratory data and facilities. The level to which BP needs to be lowered depends on the clinical diagnosis but not just the degree of hypertension. In patients with evidence of acute dysfunction/damage of target organs, it is best to provide hospital care, preferably in an intensive care unit. For less urgent situations, treatment can be given as an outpatient basis with close follow-up. Asymptomatic patients with normal clinical/laboratory findings can be managed in the emergency department and follow-up visits. Indiscriminate utilization of parenteral antihypertensive drugs should be avoided. With immediate therapeutic reduction of BP, cardiac, renal, and neurological parameters should be closely monitored. Upon the resolution of a hypertensive emergency/urgency, long-term management strategy should be outlined to prevent recurrence of the acute problem and to preserve target organ function in the long run by effective and sustained control of hypertension. Based on clinical assessment and laboratory values, work-up for secondary hypertension may be indicated in some patients with hypertensive crisis.

REFERENCES