REVIEW ARTICLE

Drugs 2008; 68 (3): 283-297
0012-6667/08/0003-0283/$53.45/0

Treatment of Acute Severe Hypertension

Current and Newer Agents

Joseph Varon[1,2,3]

1 The University of Texas Health Science Center at Houston, Houston, Texas, USA
2 The University of Texas Medical Branch at Galveston, Galveston, Texas, USA
3 St Luke's Episcopal Hospital/Texas Heart Institute, Houston, Texas, USA

Contents

Abstract

Approximately 72 million people in the US experience hypertension. Worldwide, hypertension may affect as many as 1 billion people and be responsible for ≈7.1 million deaths per year. It is estimated that ≈1% of patients with hypertension will, at some point, develop a hypertensive crisis. Hypertensive crises are further defined as either hypertensive emergencies or urgencies, depending on the degree of blood pressure elevation and presence of end-organ damage. Immediate reduction in blood pressure is required only in patients with acute end-organ damage (i.e. hypertensive emergency) and requires treatment with a titratable, short-acting, intravenous antihypertensive agent, while severe hypertension without acute end-organ damage (i.e. hypertensive urgency) is usually treated with oral antihypertensive agents.

The primary goal of intervention in a hypertensive crisis is to safely reduce blood pressure. The appropriate therapeutic approach of each patient will depend on their clinical presentation. Patients with hypertensive emergencies are best treated in an intensive care unit with titratable, intravenous, hypotensive agents. Rapid-acting intravenous antihypertensive agents are available, including labetalol, esmolol, fenoldopam, nicardipine and sodium nitroprusside. Newer agents, such as clevidipine and fenoldopam, may hold considerable advantages to other available agents in the management of hypertensive crises. Sodium nitroprusside is an extremely toxic drug and its use in the treatment of hypertensive emergencies should be avoided. Similarly, nifedipine, nitroglycerin and hydralazine should not to be considered first-line therapies in the management of hypertensive crises because these agents are associated with significant toxicities and/or adverse effects.

In the US, it is estimated that approximately 72 million people experience hypertension (defined as systolic blood pressure [SBP] >140 mmHg and/or diastolic [DBP] >90 mmHg; taking antihypertensive medication; or being told at least twice by a physician, or other health professional, that one has high blood pressure [BP]).[1] Affecting ≈30% of the US population aged >20 years old, hypertension is one of the most common chronic medical conditions,[2,3] and occurs almost twice as often in African-Americans than in Caucasians.[4-6] Moreover, the incidence of hypertension increases with age[7] and affects men at a slightly higher rate than women. Worldwide, hypertension may affect as many as 1 billion people and be responsible for ≈7.1 million deaths per year.[8]

1. Classification of Hypertension

The classification and approach to hypertension undergoes periodic review by the Joint National Committee (JNC) on Detection, Evaluation, and Treatment of High Blood Pressure.[9-15] The most recent report, JNC 7, classifies high BP in the following four stages: (i) normal; (ii) prehypertension; (iii) stage I; and (iv) stage II (table I).

The JNC 7 complete report[16,17] identifies patients with a SBP of >180 mmHg or a DBP >120 mmHg as having a 'hypertensive crisis'. This report goes on to define the operational classification of hypertensive crisis as either 'hypertensive emergencies' (i.e. severe elevations in BP [>180/120 mmHg] complicated by evidence of impending or progressive target organ dysfunction) that require immediate BP reduction (not necessarily to normal) to prevent or limit target-organ damage, or 'hypertensive urgencies' (i.e. situations associated with severe elevations in BP without progressive target-organ dysfunction).

Although not specifically addressed in the JNC 7 report, patients with a SBP >179 mmHg or a DBP >109 mmHg are usually defined as having 'severe' or 'accelerated' hypertension, and should be addressed as hypertensive crises. Accelerated hypertension is defined as a recent significant increase over baseline BP that is associated with target-organ damage. The term 'malignant hypertension', a syndrome characterized by elevated BP accompanied by encephalopathy or nephropathy,[11,14] has been used in the past; however, this term is a misnomer. Hence, it has been removed from National and International Blood Pressure Control guidelines and is

Table I. Joint National Committee (JNC)-7 classification of blood pressure for adults (reproduced from Chobanian et al.,[16] with permission)

BP classifications	Systolic BP (mmHg)	Diastolic BP (mmHg)
Normal	<120	<80
Prehypertension	120–139	80–89
Stage I	140–159	90–99
Stage II	≥160	≥100
Hypertensive crises	>180	>120

BP = blood pressure.

best referred to as a hypertensive emergency or acute severe hypertension.[14,15]

2. Hypertensive Crises

The epidemiology of hypertensive crises are similar to that of hypertension (i.e. higher among African-Americans and the elderly); however, men are affected approximately two times more frequently than women.[18-21] It is estimated that ≈1% of patients with hypertension will, at some point, develop a hypertensive crisis.[22,23]

2.1 Hypertensive Urgencies

Hypertensive urgencies are hypertensive crises associated with severe elevations in BP without progressive target-organ dysfunction.[16,17,20,24-28] Examples include upper levels of stage II hypertension associated with severe headache, shortness of breath, epistaxis or severe anxiety. The majority of these patients present as noncompliant or inadequately treated hypertensive individuals, often with little or no evidence of target-organ damage.

In patients with hypertensive urgencies, BP control can be achieved within a few hours to prevent organ damage.[25,29] Unfortunately, the term hypertensive 'urgency' has led to overly aggressive management of many patients with severe, uncomplicated hypertension. Aggressive administration of intravenous drugs or even oral agents to rapidly lower BP may be associated with significant morbidity.[30-32] Oral loading doses of antihypertensive agents can lead to cumulative effects causing hypotension. The BP of patients with hypertensive urgencies should be gradually lowered over a period of 24–48 hours, usually with oral medication.[33] Such patients may benefit from treatment with a short-acting agent, such as oral captopril, intravenous labetalol or oral clonidine,[34,35] followed by several hours of observation.[16,17] Examples of hypertensive urgencies include upper levels of stage II hypertension associated with, but not necessarily caused by, severe headache, shortness of breath, epistaxis or severe anxiety.

Table II. Examples of acute severe hypertension related conditions

Condition
Acute coronary syndrome
Acute left ventricular failure with pulmonary oedema
Acute myocardial infarction/unstable angina pectoris
Acute renal failure
Dissecting aortic aneurysm
Eclampsia
HELLP syndrome
Hypertensive encephalopathy
Intracerebral haemorrhage
Microangiopathic haemolytic anaemia
Pulmonary oedema with respiratory failure
Severe pre-eclampsia

HELLP = haemolysis, elevated liver enzymes, low platelets.

2.2 Hypertensive Emergencies

Hypertensive emergencies (i.e. acute severe hypertension) are hypertension crises characterized by severe elevations in BP (>180/120 mmHg) complicated by evidence of impending or progressive target-organ dysfunction. Organ dysfunction is uncommon with a DBP <130 mmHg (except in children and pregnancy).[33] They require immediate BP reduction (not necessarily to normal levels) to prevent or limit target-organ damage.[34,35] Examples of hypertensive crises are summarized in table II.[29,36] A SBP >169 mmHg or a DBP >109 mmHg in a pregnant woman is considered a hypertensive emergency requiring immediate pharmacological management.[37]

2.2.1 Operative and Postoperative Hypertension

In the surgical setting, a hypertensive crisis may be encountered during cardiac surgery, major vascular surgery (e.g. carotid endarterectomy, aortic surgery), neurosurgery, head and neck surgery, renal transplantation or major trauma (e.g. burns or head injury). In addition, hypertension, and hypertensive crises, are very common in the early postoperative period and are related to increased sympathetic tone and vascular resistance.[38] Postoperative hypertension (arbitrarily defined as SBP ≥190 mmHg and/or DBP ≥100 mmHg on two consecutive readings following surgery)[15,39] may have significant adverse sequelae in both cardiac and noncardiac patients. The incidence of postoperative hypertensive crises

varies depending on the population examined, being reported in 4–35% of patients shortly after the surgical procedure.[40-42] The transient nature of postoperative hypertension and the unique clinical factors present in the postoperative period require that this clinical syndrome be given individual consideration. Like other forms of accelerated hypertension, a history of hypertension is commonly seen in patients with perioperative hypertension.

2.2.2 Hypertension in Acute Stroke

Control of hypertension in patients with acute stroke is directed at maintaining adequate cerebral blood flow to minimize ischaemic damage and control of intracerebral pressure. There is currently controversy about whether or not to treat elevated BP caused by stroke as it is theorized that elevation of BP is likely to be neuroprotective. With adequate blood flow around the central area of the stroke or penumbra, cells may be salvaged.[43-46] Hence, the inappropriate lowering of the BP in acute stroke may increase neurological damage. As a result of the complexities associated with the management of hypertension in acute stroke, this subject warrants a review that is beyond the scope and size limitations of this article, and thus will not be addressed further. The reader is encouraged to consult other published literature on the subject.[47]

2.3 Pathophysiology

The pathophysiology of hypertensive crises is not fully understood, but it is thought to be due to abrupt increases in systemic vascular resistance that are likely to be related to humoral vasoconstrictors.[48,49] A hypertensive crisis can develop *de novo*, or can complicate underlying essential or secondary hypertension. The acute nature of onset suggests a triggering factor superimposed on pre-existing hypertension.[36]

With severe elevations of BP, endothelial injury occurs and fibrinoid necrosis of the arterioles ensues.[48,49] This vascular injury leads to deposition of platelets and fibrin, and a breakdown of the normal autoregulatory function. The resulting ischaemia prompts further release of vasoactive substances, completing a vicious cycle.[49]

Many patients with severe hypertension (DBP >110 mmHg) have no acute end-organ damage. Why some patients with severe hypertension develop end-organ damage (hypertensive emergency) while others do not (hypertensive urgency) remains unclear. Rapid antihypertensive therapy in the hypertensive urgency setting may be associated with significant morbidity.[30,31,50] However, there are true hypertensive emergencies in which the rapid (controlled) lowering of BP is indicated.[22,51,52]

3. Initial Management of Severe Hypertension

On initial evaluation, most patients with severe hypertension will have no evidence of end-organ damage, and thus present as hypertensive urgency. Since there is no preliminary indication of acute end-organ damage, these patients may present for evaluation of another complaint, and the elevated BP may represent an acute recognition of chronic hypertension. Utilizing oral medications, such as captopril, labetalol or clonidine, to lower the BP gradually over 24–48 hours is one approach to the management of these patients.[16,17] The use of sublingual nifedipine capsules in hypertensive emergencies should be abandoned[53] as the US FDA concluded the practice of administering sublingual/oral nifedipine was neither safe nor efficacious.[54] Rapid correction of severely elevated BP below the autoregulatory range of critical arterial beds (cerebral, coronary and renal) can result in a marked reduction in perfusion, causing ischaemia and infarction, and may be associated with significant morbidity in hypertensive urgencies or emergencies due to a shift to the right in the pressure/flow autoregulatory curve in these vascular beds.[32] BP must be reduced in these patients; however, it must be lowered in a slow and controlled fashion to prevent organ hypoperfusion. Hypertensive urgencies do not mandate admission to a hospital.

On the other hand, patients with a hypertensive emergency should be admitted to an intensive care unit (ICU) for continuous cardiac monitoring, and frequent assessment of neurological status and urine output. Altered autoregulation also occurs in pa-

tients in a hypertensive crisis, and since end-organ damage is already present, rapid and excessive correction of the BP can further reduce perfusion and propagate further injury. Therefore, patients with a hypertensive crisis are best managed with a continuous infusion of a short-acting, titratable antihypertensive agent. As a result of unpredictable pharmacodynamics, the sublingual and intramuscular route should be avoided.

According to the JNC 7 report, "The initial goal of therapy in hypertensive emergencies is to reduce mean arterial BP by no more than 25% (within minutes to 1 hour) then, if stable, to 160/100–110 mmHg within the next 2–6 hours". Advancing these guidelines, this author believes the physician would be wise to consider the immediate goal of therapy in hypertensive emergencies to reduce DBP by 10–15%, or to approximately 110 mmHg, over a period of 30–60 minutes. Sodium and volume depletion can be significant, and gentle volume expansion with an intravenous saline solution will serve to restore organ perfusion and prevent an abrupt decline in BP when antihypertensive regimens are initiated.

For those patients with the most severe clinical manifestations or with the most labile BP, intra-arterial BP monitoring may be prudent. There are a variety of rapid-acting intravenous agents that are available for use in patients with a hypertensive crisis, and the agent of choice depends on which manifestation of end-organ damage is present.

Rapid-acting intravenous agents should not be used outside of the monitored setting of an ICU to prevent steep declines of BP that may have significant morbidity or mortality. In patients with aortic dissection, the BP should be reduced rapidly (within 5–10 minutes), targeting a SBP of <120 mmHg and mean arterial pressure (MAP) of <80 mmHg.[55,56] Once stable BP control is established with intravenous agents and end-organ damage has ceased, oral therapy can be initiated as the intravenous agents are gradually down titrated. An important consideration prior to initiating intravenous therapy is to assess the patient's volume status.

3.1 Pharmacological Agents Used in the Treatment of Hypertensive Crises

A number of drugs are available for the management of hypertensive crises (see table III). The agent of choice in any particular situation will depend on the clinical presentation. The preferred agents include labetalol, esmolol, nicardipine and fenoldopam. Phentolamine and trimethaphan camsilate are less commonly used today; however, they may be useful in particular situations, such as catecholamine-induced hypertensive crises (i.e. pheochromocytoma). Sodium nitroprusside may be used in patients with acute pulmonary oedema and/or severe left ventricular dysfunction, and in patients with aortic dissection.[57] Oral and sublingual nifedipine are potentially dangerous in patients with hypertensive crises and are not recommended. Clonidine and ACE inhibitors are long acting and poorly titratable; however, these agents may be useful in the management of hypertensive urgencies. ACE inhibitors are contraindicated in pregnancy.[58,59]

Clevidipine, a third-generation, intravenous, dihydropyridine calcium-channel antagonist, is under investigation for the management of perioperative hypertension and other hypertensive crises.[60] Clevidipine is a potent arterial vasodilator with very little or no effect of the myocardial contractility and venous capacitance, in addition to minimal adverse effects. It has an extremely short half-life and is rapidly metabolized by tissue and plasma esterases. Clevidipine has the potential to protect against organ reperfusion injury through its capability to hamper oxygen free radical-mediated toxicity and cell calcium overload, and to augment endothelial nitric oxide bioavailability via antioxidative actions. As a result, clevidipine may diminish the severity of low flow myocardial ischaemia and preserve the coronary endothelial function, thereby reducing the infarct size. Because of the positive characteristics of this parenteral agent, it promises to be the drug of choice for the critical care practitioner for the strict control of BP in different clinical scenarios.[61] Currently, clevidipine is not available in the US for use outside of clinical trials.

Table III. Agents used in the management of hypertensive crises, preferred conditions and dose administration

Agent	Conditions	Administration
Enalaprilat	Congestive heart failure	IV injection of 1.25 mg over 5 min every 6 h, titrated by increments of 1.25 mg at 12- to 24-h intervals to a maximum of 5 mg every 6 h
Esmolol	Acute myocardial ischaemia[a]	Loading dose of 500–1000 μg/kg over 1 min, followed by an infusion at 25–50 μg/kg/min, which may be increased by 25 μg/kg/min every 10–20 min until the desired response to a maximum of 300 μg/kg/min
Fenoldopam	Acute myocardial ischaemia[b] Acute pulmonary oedema/diastolic dysfunction[a,c] Acute ischaemic stroke/intracerebral bleed Acute renal failure/microangiopathic anaemia Hypertensive encephalopathy Sympathetic crisis	An initial dose of 0.1 μg/kg/min, titrated by increments of 0.05–0.1 μg/kg/min to a maximum of 1.6 μg/kg/min
Labetalol	Acute aortic dissection Acute myocardial ischaemia[a] Acute ischaemic stroke/intracerebral bleed Eclampsia/pre-eclampsia Hypertensive encephalopathy	Initial bolus 20 mg, followed by boluses of 20–80 mg or an infusion starting at 1–2 mg/min and titrated until the desired hypotensive effect is achieved is particularly effective. Bolus injections of 1–2 mg/kg have been reported to produce precipitous falls in BP and should therefore be avoided; maximum cumulative dose of 300 mg over 24 h
Nicardipine	Acute myocardial ischaemiac Acute renal failure/ microangiopathic anaemia Acute ischaemic stroke/intracerebral bleed Eclampsia/pre-eclampsia Hypertensive encephalopathy Sympathetic crisis/cocaine overdose[d]	5 mg/h; titrate to effect by increasing 2.5 mg/h every 5 min to a maximum of 15 mg/h
Nitroprusside	Acute pulmonary oedema[a,c]	0.5 μg/kg/min; titrate as tolerated to maximum of 2 μg/kg/min
Hydralazine	Eclampsia	5 mg bolus then 5–10 mg IV every 20–30 min as needed
Metoprolol tartrate	Acute pulmonary oedema/diastolic dysfunction[a,c]	
Phentolamine	Sympathetic crisis Catecholamine toxicity (i.e. pheochromocytoma)	Sympathetic crisis: IV 5–20 mg Treatment of pralidoxime-induced hypertension (unlabeled use): IV 5 mg Surgery for pheochromocytoma/hypertension: IM, IV 5mg given 1–2 h before procedure and repeated as needed every 2–4 h

a In combination with nitroglycerin (up to 200 μg/min).

b May be added if pressure is controlled poorly with labetalol/esmolol alone.

c In combination with a loop diuretic.

d In combination with a benzodiazepine.

BP = blood pressure; **IM** = intramuscular; **IV** = intravenous.

The recommended intravenous antihypertensive agents currently available are reviewed briefly in sections 3.1.1 to 3.1.10. The agents are presented alphabetically by class, not in order of importance or preference.

3.1.1 Enalaprilat

Enalaprilat is an ACE inhibitor available for intravenous administration. This class of drugs has shown efficacy in the treatment of congestive heart failure, essential hypertension, and the prevention of worsening renal function in patients with diabetic and non-diabetic nephropathy. The onset of action for enalaprilat is delayed for 15 minutes, and it does not reach peak effect for ≈1 hour, while its duration of action is ≈6 hours. The effective half-life for accumulation of enalaprilat is approximately 11 hours.[62] The relatively slow onset and long duration of action make it a poor choice for use in a hypertensive crisis. In addition, ACE inhibitors have the potential to cause acute renal failure, acute renal dysfunction or hyperkalaemia in patients in circulatory decompensated states or when MAP is insufficient to support renal perfusion. Since surgical patients are at an increased risk for circulatory decom-

pensation in the post operative period, ACE inhibitors should not be considered first-line agents in the treatment of acute perioperative hypertension.

3.1.2 Labetalol

Labetalol is a combined selective α_1-adrenoceptor antagonist and nonselective β-adrenoceptor antagonist (β-blocker) with an α- to β-blocking ratio of 1 : 7.[63] Labetalol is metabolized by the liver to form an inactive glucuronide conjugate.[64] The hypotensive effect of labetalol begins within 2–5 minutes after its intravenous administration, reaching a peak at 5–15 minutes following administration and lasting for about 2–4 hours.[64,65] The elimination half-life of labetalol is approximately 5.5 hours.[66] As a result of its β-blocking effects, the heart rate is either maintained or slightly reduced. Unlike pure β-adrenergic antagonists that decrease cardiac output, labetalol maintains cardiac output.[67] Labetalol reduces the systemic vascular resistance without reducing total peripheral blood flow. In addition, the cerebral, renal and coronary blood flows are maintained.[67-70] 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.[67]

Labetalol may be administered as a loading dose of 20 mg, followed by repeated incremental doses of 20–80 mg at 10-minute intervals until the desired BP is achieved. Alternatively, after the initial loading dose, an infusion commencing at 1–2 mg/min and titrated up to until the desired hypotensive effect is achieved is particularly effective. Bolus injections of 1–2 mg/kg have been reported to produce precipitous falls in BP and should therefore be avoided.[71]

3.1.3 Esmolol

Esmolol is an ultra short-acting cardioselective, β-blocker[72-74] with an elimination half-life of ≈9 minutes.[75] Esmolol has no direct vasodilatory actions. It decreases atrial pressure by decreasing heart rate and myocardial contractility, and thus cardiac output. The onset of action of this agent is within 60 seconds, with a duration of action of 10–20 minutes;[72-74] however, because it is metabolized by red blood cell (RBC) esterases, any condition that precipitates anaemia, will prolong its 'short half-life'. The metabolism of esmolol is via rapid hydrolysis of ester linkages by RBC esterases and is not dependant on renal or hepatic function

As a result of its pharmacokinetic properties, some authors[33] consider it an 'ideal β-adrenergic blocker' for use in critically ill patients. Nonetheless, caution needs to be exercised, particularly when used in patients with chronic obstructive lung disease as this agent can precipitate bronchospasm. In addition, American College of Cardioglogy (ACC)/American Heart Association (AHA) guidelines[76] conclude it may be contraindicated for patients already on β-blocker therapy, bradycardic patients and decompensated heart failure patients, as it may compromise their myocardial function.

Esmolol is available for intravenous use both as a bolus and as an infusion. Esmolol is particularly useful in severe postoperative hypertension[77-83] and is a suitable agent in situations where cardiac output, heart rate and BP are increased. Typically, the drug is administered as a 500–1000 μg/kg loading dose over 1 minute, followed by an infusion starting at 50 μg/kg/min and increasing up to 300 μg/kg/min as necessary.

3.1.4 Clevidipine

Clevidipine is third-generation, dihydropyridine calcium-channel antagonist that has been developed for use in clinical settings where tight BP control is crucial.[61] Clevidipine is an ultra short-acting selective arteriolar vasodilator.[84,85] Clevidipine has a mean blood flow clearance of 0.105 L/kg/min and a volume of distribution of 0.51 L/kg. The half-life is around 2 minutes.[52] Clevidipine acts by selectively inhibiting the influx of extracellular calcium through the L-type channel, relaxing smooth muscle of small arteries and reducing peripheral vascular resistance.[86] Similar to esmolol, it is rapidly metabolized by RBC esterases; thus, its metabolism is not affected by renal or hepatic function. Clevidipine reduces BP by a direct and selective effect on arterioles, thereby reducing afterload without affecting cardiac filling pressures or causing reflex tachycardia.[60] Stroke volume and cardiac output usually increase. Moreover, clevidipine has been shown to

protect against ischaemia/reperfusion injury in an animal model of myocardial ischaemia, and to maintain renal function and splanchnic blood flow.[87-89]

Several small trials[90,91] have shown clevidipine to be very effective in the control of postoperative hypertension. In a recent randomized, double-blind, placebo-controlled, multicentre trial, 152 patients scheduled for cardiac surgery with current or recent hypertension were randomized to receive clevidipine or placebo preoperatively.[92] Patients received infusions of either clevidipine (0.4–8.0 μg/kg/min) or placebo (20% lipid emulsion) for at least 30 minutes. Patients treated with clevidipine demonstrated a significantly higher rate of treatment success than those in the placebo-treated group (92.5% vs 17.3%; $p < 0.0001$) and a significantly lower treatment failure rate than patients receiving placebo (7.5% vs 82.7%; $p < 0.0001$). Clevidipine achieved target BPs (SBP reduced by ≥15%) at a median of 6 minutes. Adverse events for each treatment group were similar.

Although no studies have investigated the role of this drug in hypertensive emergencies, its profile makes it a potentially ideal drug for this indication. In the author's own experience, the use of clevidipine in acute hypertension in the emergency department setting is safe and provides a predictable BP control. In addition, this drug can be safely used as an infusion for as long as 96 hours.[93]

3.1.5 Nicardipine

Nicardipine is a second-generation, dihydropyridine derivative calcium-channel antagonist with high vascular selectivity, and strong cerebral and coronary vasodilatory activity. The terminal half-life of the drug after intravenous administration to humans was about 1 hour.[94,95] The onset of action of intravenous nicardipine is from 5 to 15 minutes, with a duration of action of 4–6 hours. Intravenous nicardipine has been shown to reduce both cardiac and cerebral ischaemia.[96] The nicardipine dosage is independent of the patient's bodyweight, with an initial infusion rate of 5 mg/hour, increasing by 2.5 mg/hour every 5 minutes to a maximum of 15 mg/hour until the desired BP reduction is achieved.[33] In the author's experience, much higher doses are commonly used (e.g. 30–45 mg/hour). A useful therapeutic benefit of nicardipine is that the agent has been demonstrated to increase both stroke volume and coronary blood flow with a favourable effect on myocardial oxygen balance.[96-100] This property is useful in patients with coronary artery disease and systolic heart failure. In addition, this agent has been recommended in the AHA/American Stroke Association's guidelines for the treatment of ischaemic stroke when DBP is >120 mmHg or the SBP is >220 mmHg.[101-103] Familiar adverse effects of intravenous nicardipine are chiefly related to its antihypertensive effects; however, hypotension, as a treatment adverse effect, may be less frequent with nicardipine than with sodium nitroprusside because nicardipine does not cause venodilation.

3.1.6 Nifedipine

Nifedipine has been widely used via oral or sublingual administration in the management of hypertensive emergencies, severe hypertension associated with chronic renal failure, postoperative hypertension and pregnancy-induced hypertension. Nonetheless, the routine use of short-acting nifedipine capsules in hypertensive emergencies should be abandoned.[53] Although nifedipine has been administered via the sublingual route, the drug is poorly soluble and is not absorbed through the buccal mucosa, but is rapidly absorbed from the gastrointestinal tract after the capsule has dissolved.[104] This mode of administration has not been approved by the US FDA. The half-life of nifedipine in plasma is ≈2 hours.[105] A significant decrease in BP is usually observed 5–10 minutes after nifedipine administration, with a peak effect from 30 to 60 minutes, and a duration of action of approximately 6–8 hours.[106] Sudden, uncontrolled and severe reductions in BP accompanying the administration of nifedipine may precipitate cerebral, renal and myocardial ischaemic events that have been associated with fatal outcomes.[53] Elderly hypertensive patients with underlying organ impairment and structural vascular disease are more vulnerable to the rapid and uncontrolled reduction in arterial pressure. Given the seriousness of the reported adverse events and the lack of any clinical documentation attesting to a

benefit, the use of nifedipine capsules for hypertensive emergencies and 'pseudo emergencies' should be abandoned.[53] Over 20 years ago, the Cardiorenal Advisory Committee of the FDA concluded that the practice of administering sublingual/oral nifedipine needed to be abandoned because this agent was neither safe nor efficacious.[54] Nifedipine is not to be considered an acceptable therapy in the management of either hypertensive emergencies or urgencies.[29]

3.1.7 Fenoldopam

Fenoldopam is unique among the parenteral BP agents because it mediates peripheral vasodilation by acting on peripheral dopamine type 1 receptors. Fenoldopam is rapidly and extensively metabolized by conjugation in the liver, without participation of cytochrome P450 enzymes. The onset of action is within 5 minutes, with the maximal response being achieved by 15 minutes.[107-110] The elimination half-life of fenoldopam is ≈5 minutes,[111] with a duration of action from 30 to 60 minutes, and BP gradually returning to pretreatment values without rebound once the infusion is stopped.[107-109] No adverse effects have been reported.[107] An initial starting dose of 0.1 μg/kg/min is recommended, titrated by increments of 0.05–0.1 μg/kg/min to a maximum of 1.6 μg/kg/min. Fenoldopam improves creatinine clearance, urine flow rates and sodium excretion in severely hypertensive patients with both normal and impaired renal function.[112-114]

The use of fenoldopam as a prophylactic agent to prevent contrast-induced nephropathy has been disappointing.[115,116] Moreover, clinical studies with fenoldopam have failed to demonstrate a clinically significant reduction in death or renal replacement therapy in patients at risk for acute renal failure.[117,118] Fenoldopam causes dose-dependent increases in intraocular pressure, and its use should be avoided in patients at risk for with intraocular hypertension and intracranial hypertension. In addition, fenoldopam is in a solution that contains a sodium metabisulfate, and patients with potential sulfite sensitivity may develop acute allergic reactions.

3.1.8 Hydralazine and Diuretics

Hydralazine is a direct-acting arteriolar vasodilator, often chosen as a first-line agent for critically ill patients with pregnancy-induced hypertension. Following intramuscular or intravenous administration, there is an initial latent period of 5–15 minutes, followed by a progressive and often precipitous fall in BP that can last up to 12 hours;[119,120] however, its maximum effect is usually noted between 10 and 80 minutes. Although the circulating half-life of hydralazine is only approximately 3 hours, the half-time of its effect on BP is approximately 10 hours.[121,122] Because of the prolonged and unpredictable antihypertensive effects of hydralazine, and the inability to effectively titrate its hypotensive effect, it is best avoided in the management of hypertensive crises.

Volume depletion is common in patients with hypertensive emergencies and the administration of a diuretic together with a hypertensive agent can lead to a precipitous drop in BP. Diuretics should be avoided unless specifically indicated for volume overload, as occurs in renal parenchymal disease or coexisting pulmonary oedema. Familiar adverse effects of intravenous hydralazine include prolonged duration of action in patients with renal dysfunction, hypotension, salt retention, fluid retention, tachyphylaxis and drug-induced lupus syndrome.[123,124] Hydralazine is not to be considered an acceptable primary therapy in the management of either hypertensive emergencies or urgencies,[29] but may be a suitable adjunct therapy.

3.1.9 Nitroglycerin

Nitroglycerin is a potent venodilator and only at high doses affects arterial tone.[125] It has pharmacokinetic properties similar to sodium nitroprusside, and causes hypotension and reflex tachycardia, which are exacerbated by the volume depletion characteristic of hypertensive emergencies. Nitroglycerin reduces BP by reducing preload and cardiac output, which are undesirable effects in patients with compromised cerebral and renal perfusion. Intravenous nitroglycerin has an onset time of 2–5 minutes, duration of action of ≈10–20 minutes and is eliminated by hepatic metabolism in

≈1–4 minutes.[123,124,126] Intravenous nitroglycerin is generally not considered as a first-line therapy for hypertension as it is not as efficacious as sodium nitroprusside, may have little or no efficacy when used alone and its antihypertensive action is caused by venodilation. Low-dose administration (approximately 60 mg/min) may, however, be used as an adjunct to intravenous antihypertensive therapy in patients with hypertensive emergencies associated with acute coronary syndromes or acute pulmonary oedema. Familiar adverse effects of intravenous nitroglycerin include hypotension, hypoxaemia from ventilation perfusion mismatching, methemoglobinaemia, reflex tachycardia and tachyphylaxis.[123,124] Nitroglycerin is not to be considered an acceptable primary therapy in the management of either hypertensive emergencies or urgencies,[29] but may be a suitable adjunct therapy.

3.1.10 Sodium Nitroprusside

Sodium nitroprusside is an arterial and venous vasodilator that decreases both afterload and preload.[127,128] Sodium nitroprusside decreases cerebral blood flow while increasing intracranial pressure, effects that are particularly detrimental in patients with hypertensive encephalopathy or following a cerebrovascular accident.[129-132] In patients with coronary artery disease, a significant reduction in regional blood flow (coronary steal) can occur.[133] In a large, randomized, placebo-controlled trial,[134] sodium nitroprusside was shown to increase mortality when infused in the early hours after acute myocardial infarction (mortality at 13 weeks, 24.2% vs 12.7%). Sodium nitroprusside is a very potent agent, with an onset of action of seconds, a duration of action of 1–2 minutes and a plasma half-life of 3–4 minutes.[127] As a result of the potency, rapidity of action of this agent and the development of tachyphylaxis, we recommend intra-arterial BP monitoring. In addition, sodium nitroprusside requires special handling to prevent its degradation by light. These factors limit the use of this drug.[135]

The molecule of sodium nitroprusside contains 44% cyanide by weight.[136] Cyanide is released non-enzymatically from nitroprusside, the amount generated being dependent on the dose of sodium nitroprusside administered. Cyanide is metabolized in the liver to thiocyanate, which is 100-fold less toxic than cyanide.[136,137] The thiocyanate generated is excreted largely through the kidneys. Therefore, cyanide removal requires adequate liver function, renal function and bioavailability of thiosulfate. Thus, the use of sodium nitroprusside may cause cytotoxicity due to the release of cyanide, with interference of cellular respiration.[138,139] In the author's experience, patients can develop cyanide toxicity as early as 6–8 hours after initiation of the infusion of sodium nitroprusside. Cyanide toxicity has been documented to result in 'unexplained cardiac arrest', coma, encephalopathy, convulsions and irreversible focal neurological abnormalities.[128,138]

The current methods of monitoring for cyanide toxicity are insensitive. Metabolic acidosis is usually a preterminal event. In addition, a rise in serum thiocyanate levels is a late event and not directly related to cyanide toxicity. RBC cyanide level (although not widely available) may be a more reliable method of monitoring for cyanide toxicity.[136] An RBC cyanide level >40 nmol/mL results in detectable metabolic changes. Levels >200 nmol/mL are associated with severe clinical symptoms and levels >400 nmol/mL are considered lethal.[136] Data suggest that sodium nitroprusside infusion rates >4 μg/kg/min, for as little as 2–3 hours may lead to cyanide levels in the toxic range.[136] The recommended doses of sodium nitroprusside of up to 10 μg/kg/min results in cyanide formation at a far greater rate than humans can detoxify. Sodium nitroprusside has also been demonstrated to cause cytotoxicity through the release of nitric oxide, with hydroxyl radical and peroxynitrite generation leading to lipid peroxidation.[139-142]

Considering the potential for severe toxicity with nitroprusside, this drug should only be used when other intravenous antihypertensive agents are not available and then, only in specific clinical circumstances in patients with normal renal and hepatic function.[128] An initial starting dose should be 0.5 μg/kg/min and then titrated as tolerated. The duration of treatment should be as short as possible and the infusion rate should not be >2 μg/kg/min.

An infusion of thiosulfate should be used in patients receiving higher dosages (4–10 μg/kg/min) of sodium nitroprusside.[137]

4. Conclusion

The primary goal of intervention in a hypertensive crisis is to safely reduce BP. The appropriate therapeutic approach of each patient will depend on their clinical presentation. Safe and efficacious management of the patient experiencing hypertensive crises requires the physician to discriminate the crisis as either a hypertensive urgency or hypertensive emergency.

Rapid antihypertensive therapy is not warranted in patients with hypertensive urgencies (i.e. a hypertension crisis associated with severe elevations in BP without progressive end-organ dysfunction). Conversely, immediate BP reduction is indicated in patients experiencing hypertensive emergencies (i.e. a hypertension crisis characterized by severe elevations in BP [>180/120 mmHg] complicated by evidence of impending or progressive target-organ dysfunction) to prevent progressive end-organ damage. Hypertension associated with cerebral infarction or intracerebral haemorrhage requires treatment under special circumstances and the use of pharmacological agents must be tailored to each patient's condition. It should be noted that currently there are no widely accepted guidelines for the treatment of hypertension associated with cerebral infarction or intracerebral haemorrhage.

Patients with hypertensive emergencies are best treated in an ICU with titratable intravenous hypotensive agents. Several rapid-acting intravenous antihypertensive agents are available, including labetalol, esmolol, fenoldopam, nicardipine and sodium nitroprusside. While sodium nitroprusside is commonly used to treat severe hypertension, it is an extremely toxic drug that should be used only in rare circumstances. If the use of sodium nitroprusside cannot be avoided, it should not be used at a dose that exceeds 2 μg/kg/min. Similarly, nifedipine, nitroglycerin and hydralazine should not to be considered acceptable therapies in the management of hypertensive crises because these agents are associated with significant toxicities and/or adverse effects. Newer agents, such as clevidipine and fenoldopam, may hold considerable advantages to other available agents in the management of hypertensive crises.

Acknowledgements

The author would like to thank Dr Richard Pistolese for his assistance in the preparation and review of this article. The author did not receive support of any kind in the form of equipment, drugs or grants related to this article. The author has received honoraria for lectures from PDL Pharmaceuticals, Eli Lilly & Company and The Medicines Company, and has served as a consultant for The Medicines Company.

References

1. Rosamond W, Flegal K, Friday G, et al. Heart disease and stroke statistics: 2007 update. A report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Circulation 2007 Feb 6; 115 (5): e69-171
2. National Center for Health Statistics (U.S.). Health, United States, 2005 with chartbook on trends in the health of Americans with special feature on drugs. Hyattsville (MD), Washington, DC: Department of Health and Human Services, Centers for Disease Control and Prevention, 2005
3. Hajjar I, Kotchen TA. Trends in prevalence, awareness, treatment, and control of hypertension in the United States, 1988-2000. JAMA 2003 Jul 9; 290 (2): 199-206
4. Kearse Jr LA, Rosow C, Zaslavsky A, et al. Bispectral analysis of the electroencephalogram predicts conscious processing of information during propofol sedation and hypnosis. Anesthesiology 1998 Jan; 88 (1): 25-34
5. Burt VL, Whelton P, Roccella EJ, et al. Prevalence of hypertension in the US adult population: results from the Third National Health and Nutrition Examination Survey, 1988-1991. Hypertension 1995 Mar; 25 (3): 305-13
6. Burt VL, Cutler JA, Higgins M, et al. Trends in the prevalence, awareness, treatment, and control of hypertension in the adult US population: data from the health examination surveys, 1960 to 1991. Hypertension 1995 Jul; 26 (1): 60-9
7. Dannenberg AL, Garrison RJ, Kannel WB. Incidence of hypertension in the Framingham Study. Am J Public Health 1988 Jun; 78 (6): 676-9
8. WHO. Reducing risks, promoting healthy life: the world health report. Geneva: World Health Organization, 2002
9. Report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure: a cooperative study. JAMA 1977 Jan 17; 237 (3): 255-61
10. The 1980 report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure. Arch Intern Med 1980 Oct; 140 (10): 1280-5
11. The 1984 report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure. Arch Intern Med 1984 May; 144 (5): 1045-57
12. The 1988 report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure. Arch Intern Med 1988 May; 148 (5): 1023-38
13. The fifth report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure. Arch Intern Med 1993 Jan 25; 153 (2): 154-83

14. The sixth report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Arch Intern Med 1997 Nov 24; 157 (21): 2413-46
15. Chobanian AV, Bakris GL, Black HR, et al. The seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. JAMA 2003 May 21; 289 (19): 2560-72
16. Chobanian AV, Bakris GL, Black HR, et al. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Hypertension 2003 Dec; 42 (6): 1206-52
17. Joint National Committee on Detection Evaluation and Treatment of High Blood Pressure, National High Blood Pressure Education Program Coordinating Committee. The seventh report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure, JNC7 (complete report). NIH Publication No. 04-5230. Bethesda (MD): National Heart, Lung, and Blood Institute, Health Information Center, 2004
18. Lip GY, Beevers M, Potter JF, et al. Malignant hypertension in the elderly. QJM 1995 Sep; 88 (9): 641-7
19. Smith CB, Flower LW, Reinhardt CE. Control of hypertensive emergencies. Postgrad Med 1991 Apr; 89 (5): 111-6, 9
20. Kaplan NM. Treatment of hypertensive emergencies and urgencies. Heart Dis Stroke 1992 Nov-Dec; 1 (6): 373-8
21. Bennett NM, Shea S. Hypertensive emergency: case criteria, sociodemographic profile, and previous care of 100 cases. Am J Public Health 1988 Jun; 78 (6): 636-40
22. McRae Jr RP, Liebson PR. Hypertensive crisis. Med Clin North Am 1986 Jul; 70 (4): 749-67
23. Vidt DG. Current concepts in treatment of hypertensive emergencies. Am Heart J 1986 Jan; 111 (1): 220-5
24. Gifford Jr RW. Management of hypertensive crises. JAMA 1991 Aug 14; 266 (6): 829-35
25. Calhoun DA, Oparil S. Treatment of hypertensive crisis. N Engl J Med 1990 Oct 25; 323 (17): 1177-83
26. Rahn KH. How should we treat a hypertensive emergency? Am J Cardiol 1989 Feb 2; 63 (6): 48-50C
27. Reuler JB, Magarian GJ. Hypertensive emergencies and urgencies: definition, recognition, and management. J Gen Intern Med 1988 Jan-Feb; 3 (1): 64-74
28. Ferguson RK, Vlasses PH. Hypertensive emergencies and urgencies. JAMA 1986 Mar 28; 255 (12): 1607-13
29. Varon J, Marik PE. Clinical review: the management of hypertensive crises. Crit Care 2003 Oct; 7 (5): 374-84
30. Bertel O, Marx BE, Conen D. Effects of antihypertensive treatment on cerebral perfusion. Am J Med 1987 Mar 30; 82 (3B): 29-36
31. Bannan LT, Beevers DG, Wright N. ABC of blood pressure reduction: emergency reduction, hypertension in pregnancy, and hypertension in the elderly. BMJ 1980 Oct 25; 281 (6248): 1120-2
32. Strandgaard S, Olesen J, Skinhoj E, et al. Autoregulation of brain circulation in severe arterial hypertension. BMJ 1973 Mar 3; 1 (5852): 507-10
33. Varon J, Marik PE. The diagnosis and management of hypertensive crises. Chest 2000 Jul; 118 (1): 214-27
34. Greene CS, Gretler DD, Cervenka K, et al. Cerebral blood flow during the acute therapy of severe hypertension with oral clonidine. Am J Emerg Med 1990 Jul; 8 (4): 293-6
35. Houston MC. The comparative effects of clonidine hydrochloride and nifedipine in the treatment of hypertensive crises. Am Heart J 1988 Jan; 115 (1 Pt 1): 152-9
36. Marik PE, Varon J. Hypertensive crises: challenges and management. Chest 2007 Jun; 131 (6): 1949-62
37. Rey E, LeLorier J, Burgess E, et al. Report of the Canadian Hypertension Society Consensus Conference: 3. Pharmacologic treatment of hypertensive disorders in pregnancy. CMAJ 1997 Nov 1; 157 (9): 1245-54
38. Alper A, Calhoun D. Hypertensive emergencies. In: Antman EM, editor. Cardiovascular therapeutics: a companion to Braunwald's Heart disease. 2nd ed. Philadelphia (PA): W.B. Saunders Co., 2002: 817-31
39. Plets C. Arterial hypertension in neurosurgical emergencies. Am J Cardiol 1989 Feb 2; 63 (6): 40-2C
40. Halpern NA, Alicea M, Krakoff LR, et al. Postoperative hypertension: a prospective, placebo-controlled, randomized, double-blind trial, with intravenous nicardipine hydrochloride. Angiology 1990 Nov; 41 (11 Pt 2): 992-1004
41. Prys-Rroberts C. Anaesthesia and hypertension. Br J Anaesth 1984 Jul; 56 (7): 711-24
42. Gal TJ, Cooperman LH. Hypertension in the immediate postoperative period. Br J Anaesth 1975 Jan; 47 (1): 70-4
43. Lisk DR, Grotta JC, Lamki LM, et al. Should hypertension be treated after acute stroke? A randomized controlled trial using single photon emission computed tomography. Arch Neurol 1993 Aug; 50 (8): 855-62
44. Brott T, Lu M, Kothari R, et al. Hypertension and its treatment in the NINDS rt-PA Stroke Trial. Stroke 1998 Aug; 29 (8): 1504-9
45. Leonardi-Bee J, Bath PM, Phillips SJ, et al. Blood pressure and clinical outcomes in the International Stroke Trial. Stroke 2002 May; 33 (5): 1315-20
46. Oliveira-Filho J, Silva SC, Trabuco CC, et al. Detrimental effect of blood pressure reduction in the first 24 hours of acute stroke onset. Neurology 2003 Oct 28; 61 (8): 1047-51
47. Varon J. Diagnosis and management of labile blood pressure during acute cerebrovascular accidents and other hypertensive crises. Ann Emerg Med 2007; 25: 949-59
48. Ault MJ, Ellrodt AG. Pathophysiological events leading to the end-organ effects of acute hypertension. Am J Emerg Med 1985 Dec; 3 (6 Suppl.): 10-5
49. Wallach R, Karp RB, Reves JG, et al. Pathogenesis of paroxysmal hypertension developing during and after coronary bypass surgery: a study of hemodynamic and humoral factors. Am J Cardiol 1980 Oct; 46 (4): 559-65
50. Reed WG, Anderson RJ. Effects of rapid blood pressure reduction on cerebral blood flow. Am Heart J 1986 Jan; 111 (1): 226-8
51. Chen K, Varon J, Wenker OC, et al. Acute thoracic aortic dissection: the basics. J Emerg Med 1997 Nov-Dec; 15 (6): 859-67
52. Garcia Jr JY, Vidt DG. Current management of hypertensive emergencies. Drugs 1987 Aug; 34 (2): 263-78
53. Grossman E, Messerli FH, Grodzicki T, et al. Should a moratorium be placed on sublingual nifedipine capsules given for hypertensive emergencies and pseudoemergencies? JAMA 1996 Oct; 276 (16): 1328-31
54. Levy JH. Treatment of perioperative hypertension. Anesthesiol Clin North Am 1999; 17 (3): 567-80
55. Estrera AL, Miller 3rd CC, Safi HJ, et al. Outcomes of medical management of acute type B aortic dissection. Circulation 2006 Jul 4; 114 (1 Suppl.): I384-9
56. Khan IA, Nair CK. Clinical, diagnostic, and management perspectives of aortic dissection. Chest 2002 Jul; 122 (1): 311-28

57. Khot UN, Novaro GM, Popovic ZB, et al. Nitroprusside in critically ill patients with left ventricular dysfunction and aortic stenosis. N Engl J Med 2003 May 1; 348 (18): 1756-63
58. DiPette DJ, Ferraro JC, Evans RR, et al. Enalaprilat, an intravenous angiotensin-converting enzyme inhibitor, in hypertensive crises. Clin Pharmacol Ther 1985 Aug; 38 (2): 199-204
59. Hirschl MM, Binder M, Bur A, et al. Impact of the renin-angiotensin-aldosterone system on blood pressure response to intravenous enalaprilat in patients with hypertensive crises. J Hum Hypertens 1997 Mar; 11 (3): 177-83
60. Nordlander M, Bjorkman JA, Regard HCG, et al. Pharmacokinetics and hemodynamic effects of an ultrashort-acting calcium antagonist [abstract]. Br J Anaesth 1996; 76 Suppl.: A24
61. Rodríguez G, Varon J. Clevidipine. A unique agent for the critical care practitioner. Crit Care Shock 2006 May; 9 (2): 37-41
62. Merck & Co. I. Vasotec® I.V.(enalaprilat) prescribing information [online]. Available from URL: http://www.fda.gov/cder/foi/label/2001/19309s23lbl.pdf. [Accessed 2007 Jul 16]
63. Lund-Johansen P. Pharmacology of combined alpha-beta-blockade: II. Haemodynamic effects of labetalol. Drugs 1984; 28 Suppl. 2: 35-50
64. Kanto J, Allonen H, Kleimola T, et al. Pharmacokinetics of labetalol in healthy volunteers. Int J Clin Pharmacol Ther Toxicol 1981 Jan; 19 (1): 41-4
65. Goldberg ME, Clark S, Joseph J, et al. Nicardipine versus placebo for the treatment of postoperative hypertension. Am Heart J 1990 Feb; 119 (2 Pt 2): 446-50
66. Bedford Laboratories. Labetolol HCL injection USP prescribing information [online]. Available from URL: http://www.bedfordlabs.com/products/inserts/LBTL-P02.pdf [Accessed 2007 Jul 16]
67. Pearce CJ, Wallin JD. Labetalol and other agents that block both alpha- and beta-adrenergic receptors. Cleve Clin J Med 1994 Jan-Feb; 61 (1): 59-69; quiz 80-2
68. Marx PG, Reid DS. Labetalol infusion in acute myocardial infarction with systemic hypertension. Br J Clin Pharmacol 1979; 8 Suppl. 2: 233-8S
69. Olsen KS, Svendsen LB, Larsen FS, et al. Effect of labetalol on cerebral blood flow, oxygen metabolism and autoregulation in healthy humans. Br J Anaesth 1995 Jul; 75 (1): 51-4
70. Wallin JD. Adrenoreceptors and renal function. J Clin Hypertens 1985 Jun; 1 (2): 171-8
71. Rosei EA, Trust PM, Brown JJ, et al. Intravenous labetalol in severe hypertension [letter]. Lancet 1975 Nov 29; II (7944): 1093-4
72. Gray RJ. Managing critically ill patients with esmolol: an ultra short-acting beta-adrenergic blocker. Chest 1988 Feb; 93 (2): 398-403
73. Lowenthal DT, Porter RS, Saris SD, et al. Clinical pharmacology, pharmacodynamics and interactions with esmolol. Am J Cardiol 1985 Oct 23; 56 (11): 14-8F
74. Reynolds RD, Gorczynski RJ, Quon CY. Pharmacology and pharmacokinetics of esmolol. J Clin Pharmacol 1986 Mar; 26 Suppl. A: A3-14
75. Bedford Laboratories. Esmolol HCL injection prescribing information [online]. Available from URL: http://www.bedfordlabs.com/products/inserts/esmolol_pi.pdf [Accessed 2007 Jul 16]
76. Hunt SA, Abraham WT, Chin MH, et al. ACC/AHA 2005 guideline update for the diagnosis and management of chronic heart failure in the adult: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2001 Guidelines for the Evaluation and Management of Heart Failure). Developed in collaboration with the American College of Chest Physicians and the International Society for Heart and Lung Transplantation: endorsed by the Heart Rhythm Society. Circulation 2005 Sep 20; 112 (12): e154-235
77. Balser JR, Martinez EA, Winters BD, et al. Beta-adrenergic blockade accelerates conversion of postoperative supraventricular tachyarrhythmias. Anesthesiology 1998 Nov; 89 (5): 1052-9
78. Platia EV, Michelson EL, Porterfield JK, et al. Esmolol versus verapamil in the acute treatment of atrial fibrillation or atrial flutter. Am J Cardiol 1989 Apr 15; 63 (13): 925-9
79. Stumpf JL. Drug therapy of hypertensive crises. Clin Pharm 1988 Aug; 7 (8): 582-91
80. Smerling A, Gersony WM. Esmolol for severe hypertension following repair of aortic coarctation. Crit Care Med 1990 Nov; 18 (11): 1288-90
81. Gray RJ, Bateman TM, Czer LS, et al. Use of esmolol in hypertension after cardiac surgery. Am J Cardiol 1985 Oct 23; 56 (11): 49-56F
82. Gray RJ, Bateman TM, Czer LS, et al. Comparison of esmolol and nitroprusside for acute post-cardiac surgical hypertension. Am J Cardiol 1987 Apr 1; 59 (8): 887-91
83. Muzzi DA, Black S, Losasso TJ, et al. Labetalol and esmolol in the control of hypertension after intracranial surgery. Anesth Analg 1990 Jan; 70 (1): 68-71
84. Bailey JM, Lu W, Levy JH, et al. Clevidipine in adult cardiac surgical patients: a dose-finding study. Anesthesiology 2002 May; 96 (5): 1086-94
85. Ericsson H, Fakt C, Jolin-Mellgard A, et al. Clinical and pharmacokinetic results with a new ultrashort-acting calcium antagonist, clevidipine, following gradually increasing intravenous doses to healthy volunteers. Br J Clin Pharmacol 1999 May; 47 (5): 531-8
86. Ericsson H, Tholander B, Regardh CG. In vitro hydrolysis rate and protein binding of clevidipine, a new ultrashort-acting calcium antagonist metabolised by esterases, in different animal species and man. Eur J Pharm Sci 1999 Apr; 8 (1): 29-37
87. Segawa D, Sjoquist PO, Wang QD, et al. Calcium antagonist protects the myocardium from reperfusion injury by interfering with mechanisms directly related to reperfusion: an experimental study with the ultrashort-acting calcium antagonist clevidipine. J Cardiovasc Pharmacol 2000 Sep; 36 (3): 338-43
88. Segawa D, Sjoquist PO, Wang QD, et al. Time-dependent cardioprotection with calcium antagonism and experimental studies with clevidipine in ischemic-reperfused pig hearts: part II. J Cardiovasc Pharmacol 2002 Sep; 40 (3): 339-45
89. Stephens CT, Jandhyala BS. Effects of fenoldopam, a dopamine D-1 agonist, and clevidipine, a calcium channel antagonist, in acute renal failure in anesthetized rats. Clin Exp Hypertens 2002 May; 24 (4): 301-13
90. Kieler-Jensen N, Jolin-Mellgard A, Nordlander M, et al. Coronary and systemic hemodynamic effects of clevidipine, an ultra-short-acting calcium antagonist, for treatment of hypertension after coronary artery surgery. Acta Anaesthesiol Scand 2000 Feb; 44 (2): 186-93
91. Powroznyk AV, Vuylsteke A, Naughton C, et al. Comparison of clevidipine with sodium nitroprusside in the control of blood pressure after coronary artery surgery. Eur J Anaesthesiol 2003 Sep; 20 (9): 697-703
92. Levy JH, Mancao MY, Gitter R, et al. Clevidipine Effectively and rapidly controls blood pressure preoperatively in cardiac surgery patients: the results of the randomized, placebo-con-

trolled efficacy study of clevidipine assessing its preoperative antihypertensive effect in cardiac surgery-1. Anesth Analg. In press
93. Varon J, Peacock W, Garrison N, et al. Prolonged infusion of clevidipine results in safe and predictable blood pressure control in patients with acute severe hypertension. Chest 2007; 132 (4): 477S
94. Higuchi S, Shiobara Y. Comparative pharmacokinetics of nicardipine hydrochloride, a new vasodilator, in various species. Xenobiotica 1980 Jun; 10 (6): 447-54
95. PDL BioPharma I. Cardene® (nicardipine HCl) prescribing information [online]. Available from URL: http://www.cardeneiv.info/Cardene_Full_PI.pdf [Accessed 2007 Jul 16]
96. Schillinger D. Nifedipine in hypertensive emergencies: a prospective study. J Emerg Med 1987 Nov-Dec; 5 (6): 463-73
97. Lambert CR, Hill JA, Feldman RL, et al. Effects of nicardipine on left ventricular function and energetics in man. Int J Cardiol 1986 Mar; 10 (3): 237-50
98. Lambert CR, Hill JA, Feldman RL, et al. Effects of nicardipine on exercise- and pacing-induced myocardial ischemia in angina pectoris. Am J Cardiol 1987 Sep 1; 60 (7): 471-6
99. Lambert CR, Hill JA, Nichols WW, et al. Coronary and systemic hemodynamic effects of nicardipine. Am J Cardiol 1985 Mar 1; 55 (6): 652-6
100. Vincent JL, Berlot G, Preiser JC, et al. Intravenous nicardipine in the treatment of postoperative arterial hypertension. J Cardiothorac Vasc Anesth 1997 Apr; 11 (2): 160-4
101. Broderick J, Connolly S, Feldmann E, et al. Guidelines for the management of spontaneous intracerebral hemorrhage in adults: 2007 update. A guideline from the American Heart Association/American Stroke Association Stroke Council, High Blood Pressure Research Council, and the Quality of Care and Outcomes in Research Interdisciplinary Working Group. Stroke 2007 Jun; 38 (6): 2001-23
102. Adams H, Adams R, Del Zoppo G, et al. Guidelines for the early management of patients with ischemic stroke: 2005 guidelines update. A scientific statement from the Stroke Council of the American Heart Association/American Stroke Association. Stroke 2005 Apr; 36 (4): 916-23
103. Adams Jr HP, Adams RJ, Brott T, et al. Guidelines for the early management of patients with ischemic stroke: a scientific statement from the Stroke Council of the American Stroke Association. Stroke 2003 Apr; 34 (4): 1056-83
104. van Harten J, Burggraaf K, Danhof M, et al. Negligible sublingual absorption of nifedipine. Lancet 1987 Dec 12; II (8572): 1363-5
105. Pfizer Labs. Procardia® (nifedipine) prescribing information [online]. Available from URL: http://www.pfizer.com/pfizer/download/uspi_procardia.pdf [Accessed 2007 Jul 16]
106. Huysmans FT, Sluiter HE, Thien TA, et al. Acute treatment of hypertensive crisis with nifedipine. Br J Clin Pharmacol 1983 Dec; 16 (6): 725-7
107. Bodmann KF, Troster S, Clemens R, et al. Hemodynamic profile of intravenous fenoldopam in patients with hypertensive crisis. Clin Investig 1993 Dec; 72 (1): 60-4
108. Munger MA, Rutherford WF, Anderson L, et al. Assessment of intravenous fenoldopam mesylate in the management of severe systemic hypertension. Crit Care Med 1990 May; 18 (5): 502-4
109. White WB, Radford MJ, Gonzalez FM, et al. Selective dopamine-1 agonist therapy in severe hypertension: effects of intravenous fenoldopam. J Am Coll Cardiol 1988 May; 11 (5): 1118-23
110. Weber RR, McCoy CE, Ziemniak JA, et al. Pharmacokinetic and pharmacodynamic properties of intravenous fenoldopam, a dopamine1-receptor agonist, in hypertensive patients. Br J Clin Pharmacol 1988 Jan; 25 (1): 17-21
111. Bedford Laboratories. Fenoldopam mesylate injection USP prescribing information [online]. Available from URL: http://www.bedfordlabs.com/products/inserts/fenoldopam_pi.pdf [Accessed 2007 Jul 16]
112. Shusterman NH, Elliott WJ, White WB. Fenoldopam, but not nitroprusside, improves renal function in severely hypertensive patients with impaired renal function. Am J Med 1993 Aug; 95 (2): 161-8
113. Elliott WJ, Weber RR, Nelson KS, et al. Renal and hemodynamic effects of intravenous fenoldopam versus nitroprusside in severe hypertension. Circulation 1990 Mar; 81 (3): 970-7
114. White WB, Halley SE. Comparative renal effects of intravenous administration of fenoldopam mesylate and sodium nitroprusside in patients with severe hypertension. Arch Intern Med 1989 Apr; 149 (4): 870-4
115. Ng TM, Shurmur SW, Silver M, et al. Comparison of N-acetylcysteine and fenoldopam for preventing contrast-induced nephropathy (CAFCIN). Int J Cardiol 2006 May 24; 109 (3): 322-8
116. Pannu N, Wiebe N, Tonelli M. Prophylaxis strategies for contrast-induced nephropathy. JAMA 2006 Jun 21; 295 (23): 2765-79
117. Tumlin JA, Finkel KW, Murray PT, et al. Fenoldopam mesylate in early acute tubular necrosis: a randomized, double-blind, placebo-controlled clinical trial. Am J Kidney Dis 2005 Jul; 46 (1): 26-34
118. Landoni G, Biondi-Zoccai GG, Tumlin JA, et al. Beneficial impact of fenoldopam in critically ill patients with or at risk for acute renal failure: a meta-analysis of randomized clinical trials. Am J Kidney Dis 2007 Jan; 49 (1): 56-68
119. Schroeder HA. Effects on hypertension of sulfhydryl and hydrazine compounds. J Clin Invest 1951 Nov; 30 (5): 672-3
120. Shepherd AM, Ludden TM, McNay JL, et al. Hydralazine kinetics after single and repeated oral doses. Clin Pharmacol Ther 1980 Dec; 28 (6): 804-11
121. Ludden TM, Shepherd AM, McNay JL, et al. Hydralazine kinetics in hypertensive patients after intravenous administration. Clin Pharmacol Ther 1980 Dec; 28 (6): 736-42
122. O'Malley K, Segal JL, Israili ZH, et al. Duration of hydralazine action in hypertension. Clin Pharmacol Ther 1975 Nov; 18 (5 Pt 1): 581-6
123. Gerber JG, Nies AS. Antihypertensive agents and the drug therapy of hypertension. In: Goodman LS, Gilman A, Gilman AG, editors. Goodman and Gilman's the pharmacological basis of therapeutics. 8th ed. New York (NY): Pergamon Press, 1990: 784-813
124. Straka RJ, Lohr B, Borchardt-Phelps P, et al. Antihypertensive agents. In: Irwin RS, Cerra FB, Rippe JM, editors. Intensive care medicine. 3rd ed. Boston (MA): Little Brown, 1996: 2286-317
125. Bussmann WD, Kenedi P, von Mengden HJ, et al. Comparison of nitroglycerin with nifedipine in patients with hypertensive crisis or severe hypertension. Clin Investig 1992 Dec; 70 (12): 1085-8
126. Parke Davis Pharmaceuticals Ltd. Nitrostat® (nitroglycerin tablets, USP) prescribing information [online]. Available from URL: http://www.pfizer.com/pfizer/download/uspi_nitrostat.pdf [Accessed 2007 Jul 16]

127. Friederich JA, Butterworth JFT. Sodium nitroprusside: twenty years and counting. Anesth Analg 1995 Jul; 81 (1): 152-62
128. Robin ED, McCauley R. Nitroprusside-related cyanide poisoning: time (long past due) for urgent, effective interventions. Chest 1992 Dec; 102 (6): 1842-5
129. Hartmann A, Buttinger C, Rommel T, et al. Alteration of intracranial pressure, cerebral blood flow, autoregulation and carbondioxide-reactivity by hypotensive agents in baboons with intracranial hypertension. Neurochirurgia (Stuttg) 1989 Mar; 32 (2): 37-43
130. Kondo T, Brock M, Bach H. Effect of intra-arterial sodium nitroprusside on intracranial pressure and cerebral autoregulation. Jpn Heart J 1984 Mar; 25 (2): 231-7
131. Griswold WR, Reznik V, Mendoza SA. Nitroprusside-induced intracranial hypertension. JAMA 1981 Dec 11; 246 (23): 2679-80
132. Anile C, Zanghi F, Bracali A, et al. Sodium nitroprusside and intracranial pressure. Acta Neurochir (Wien) 1981; 58 (3-4): 203-11
133. Mann T, Cohn PF, Holman LB, et al. Effect of nitroprusside on regional myocardial blood flow in coronary artery disease: results in 25 patients and comparison with nitroglycerin. Circulation 1978 Apr; 57 (4): 732-8
134. Cohn JN, Franciosa JA, Francis GS, et al. Effect of short-term infusion of sodium nitroprusside on mortality rate in acute myocardial infarction complicated by left ventricular failure: results of a Veterans Administration cooperative study. N Engl J Med 1982 May 13; 306 (19): 1129-35
135. Tumlin JA, Dunbar LM, Oparil S, et al. Fenoldopam, a dopamine agonist, for hypertensive emergency: a multicenter randomized trial. Fenoldopam Study Group. Acad Emerg Med 2000 Jun; 7 (6): 653-62
136. Pasch T, Schulz V, Hoppelshauser G. Nitroprusside-induced formation of cyanide and its detoxication with thiosulfate during deliberate hypotension. J Cardiovasc Pharmacol 1983 Jan-Feb; 5 (1): 77-85
137. Hall VA, Guest JM. Sodium nitroprusside-induced cyanide intoxication and prevention with sodium thiosulfate prophylaxis. Am J Crit Care 1992 Sep; 1 (2): 19-25; quiz 6-7
138. Izumi Y, Benz AM, Clifford DB, et al. Neurotoxic effects of sodium nitroprusside in rat hippocampal slices. Exp Neurol 1993 May; 121 (1): 14-23
139. Niknahad H, O'Brien PJ. Involvement of nitric oxide in nitroprusside-induced hepatocyte cytotoxicity. Biochem Pharmacol 1996 Apr 26; 51 (8): 1031-9
140. Gobbel GT, Chan TY, Chan PH. Nitric oxide- and superoxide-mediated toxicity in cerebral endothelial cells. J Pharmacol Exp Ther 1997 Sep; 282 (3): 1600-7
141. Nakamura Y, Yasuda M, Fujimori H, et al. Cytotoxic effect of sodium nitroprusside on PC12 cells. Chemosphere 1997 Feb; 34 (2): 317-24
142. Rauhala P, Khaldi A, Mohanakumar KP, et al. Apparent role of hydroxyl radicals in oxidative brain injury induced by sodium nitroprusside. Free Radic Biol Med 1998 May; 24 (7-8): 1065-73

Correspondence: Professor *Joseph Varon*, 2219 Dorrington St, Houston, TX 77030-3209, USA.
E-mail: Joseph.Varon@uth.tmc.edu