Clinical evidence of efficacy and safety of i.v. antihypertensives

Hypertensive emergencies. End-organ systems are affected by the excessive BP levels seen in hypertensive emergencies. Patients require rapid treatment to prevent or minimize organ damage and are best treated with i.v. medications in environments with appropriate monitoring systems. While patients with hypertensive urgency also require therapeutic intervention, they can often be managed with oral therapy, gradually lowering BP levels toward normal levels.

Hypertension may exist with conditions where particular treatments have demonstrated benefits on the natural history of the disease. Compelling indications for specific therapy involve high-risk conditions that can be direct sequelae of hypertension (heart failure, ischemic heart disease, chronic kidney disease, recurrent stroke) or are commonly associated with hypertension (diabetes, high coronary disease risk).96

Therapeutic decisions should focus on the end-organ system at risk and the effect of the available i.v. agents on that system.96

A number of studies have evaluated the i.v. antihypertensives for hypertensive emergency. Yang et al.97 compared i.v. nicardipine with i.v. 

---

Intravenous therapy for hypertensive emergencies, part 2

DENISE RHONEY AND W. FRANK PEACOCK

Purpose. Intravenous antihypertensive agents for the treatment of hypertensive emergencies are reviewed.

Summary. An estimated 500,000 people in the United States experience a hypertensive crisis annually. Hypertensive emergency is associated with significant morbidity in the form of end-organ damage. Rapid controlled reduction of blood pressure (BP) may be necessary to prevent or minimize end-organ damage. I.V. antihypertensive agents available for the treatment of hypertensive emergencies are, in general, characterized by a short onset and offset of action and predictable responses during dosage adjustments to reach BP goals, without excessive adjustment or extreme fluctuations in BP. Nicardipine, nitroprusside, fenoldopam, nitroglycerin, enalaprilat, hydralazine, labetalol, esmolol, and phentolamine are i.v. antihypertensive agents recommended for use in hypertensive emergency by the seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Since the publication of these recommendations, another i.v. antihypertensive agent, clevidipine, became commercially available. The selection of a specific agent should be based on the agent’s pharmacology and patient-specific factors, such as comorbidity and the presence of end-organ damage.

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

Index terms: Clevidipine; Drugs; Emergencies; Enalaprilat; Esmolol; Fenoldopam; Hydralazine; Hypertension; Hypotensive agents; Injections; Labetalol; Nicardipine; Nitroglycerin; Nitroprusside; Phentolamine
sodium nitroprusside for the treatment of hypertensive emergency in a randomized trial of 40 patients. Significant reductions in SBP and DBP were observed in both groups, with no significant time-dependent differences between groups. Patients randomized to nicardipine had a greater drop in noradrenaline levels compared with patients treated with sodium nitroprusside. The authors concluded that nicardipine was as effective as sodium nitroprusside for the treatment of hypertensive emergency, without the concern of thiocyanate toxicity. A similar, larger study in 121 patients found similar reductions in SBP and DBP levels in patients randomized to i.v. nicardipine or sodium nitroprusside.88 The mean time to therapeutic response was 60 minutes in both study groups. The frequency of significant hypotension (BP level of <100/50 mm Hg) occurred in fewer patients randomized to i.v. nicardipine (n = 2) compared with patients treated with sodium nitroprusside (n = 10) (p < 0.05). In addition, fewer dosage adjustments were required to achieve the target BP in the nicardipine group versus the sodium nitroprusside group.

In studies comparing fenoldopam with sodium nitroprusside, the magnitude of BP reduction was similar in patients with severe acute hypertension,82,99 as was the time to achieve the target BP. Fenoldopam was also associated with significant increases in urinary output, sodium excretion, and creatinine clearance, whereas patients treated with sodium nitroprusside had slight decreases in these values.82,100 Fenoldopam has also been studied in patients with hypertensive emergencies and evidence of end-organ damage, where it effectively and rapidly lowered BP and was found to be safe in this setting.101 An open-label, single-group, multicenter study was conducted to evaluate the effect of clevidipine in 126 patients with acute hypertension (mean baseline SBP, 202 mm Hg) in the emergency department.102 The study included patients classified as having both hypertensive urgency and emergency. Long-term administration of clevidipine was evaluated for each patient (mean duration of infusion, 21.3 hours). Investigators determined a target SBP range (20–40 mm Hg from upper to lower limits) to be achieved within the first 30 minutes of clevidipine infusion initiation. The initial infusion rate was 2 mg/hr (4 mL/hr). Doses were then increased in doubling increments every 3 minutes, not to exceed 32 mg/hr, until the prespecified SBP was achieved. The mean infusion rate was 9.52 mg/hr, with a mean maximum infusion rate of 17.5 mg/hr. The median time to reach the target BP range was 10.9 minutes; within 30 minutes of starting the infusion, 88.9% of patients achieved the BP goal. By 18 hours (the minimum length of infusion defined by the study), SBP had been reduced by a mean of 26% from baseline. Most patients (90.5%) were treated with clevidipine only. Successful transition to oral therapy (defined as SBP remaining within the target range at 6 hours after discontinuation of the clevidipine infusion) was accomplished in 91.3% of the patients. The most commonly reported adverse effects in this trial were headache (6.3%), nausea (4.8%), chest discomfort (3.2%), and vomiting (3.2%). Triglyceride levels were also evaluated 6 hours after infusion termination, and no differences were observed compared with baseline. A significant limitation of this open-label study was the inclusion of patients with both hypertensive urgency and hypertensive emergency.103

Labetalol decreased BP by ≥30 mm Hg in 15 of 17 patients with severe hypertension (DBP of ≥125 mm Hg) without reflex tachycardia.104 An initial injection of 20 mg was given over 2 minutes; additional injections of 40–80 mg were given at 10-minute intervals until supine SBP decreased by >30 mm Hg or until 300 mg of labetalol was given. Adverse effects were mild and brief. No neurologic deterioration, hypotension, or coronary insufficiency occurred. The authors concluded that labetalol was a suitable alternative to direct-acting vasodilator agents for use in the management of patients with hypertensive emergencies.

**Ischemic stroke.** Appropriate management of BP following acute ischemic stroke (AIS) remains controversial. Hypertension during an ischemic stroke is extremely common, with BP spontaneously decreasing within a few days after stroke.105,106 The relationship between the BP elevation and patient outcomes is unclear, with much conflicting data. In the National Institutes of Neurological Disorders and Stroke recombinant tissue plasminogen activator (rt-PA) stroke trial,107 patients with hypertensive rt-PA who received acute antihypertensive therapy (i.v. nitroprusside, nicardipine, labetalol, or hydralazine; sublingual nifedipine; or extended-release or topical nitroglycerin) were less likely to have favorable outcomes at three months than were patients with hypertensive rt-PA who did not receive antihypertensive therapy. The authors could not rule out that treating elevated BP may be associated with worse outcomes by an unknown mechanism in some patient populations. Some studies have shown an association between elevated BP and poor outcomes,108,109 while others have found that higher BP is associated with less neurologic deterioration.110 Several studies have demonstrated a “U-shaped” relationship between BP and outcome, where both very high BP and very low BP are associated with poor outcomes.111–113 Stead et al.114 reported increased mortality associated with an SBP of <155 mm Hg and of >220 mm Hg and a DBP of <70 mm Hg and of >105 mm Hg.
The concern with lowering BP in ischemic stroke is the expansion of the central ischemic core by worsening hypoperfusion within the ischemic penumbra since this area may have disrupted autoregulation. There are limited studies that have evaluated the effect of BP lowering and optimal pharmacologic interventions following AIS. The Stroke Council of the American Heart Association has provided recommendations for lowering BP based on a patient’s eligibility to receive thrombolysis. In thrombolysis candidates, i.v. therapy is indicated when SBP exceeds 185 mm Hg or DBP exceeds 110 mm Hg. These guidelines suggest that nicardipine infusion, labetalol given as an i.v. bolus (may repeat once) or nitroglycerin ointment be used in this setting (Appendix A). In patients who are not thrombolysis candidates, the guidelines recommend a threshold for initiating i.v. antihypertensives (nicardipine or labetalol) of an SBP of >220 mm Hg and a DBP of >120 mm Hg. Unless other evidence of end-organ damage is present, the goal is to lower BP by 15–25% within the first 24 hours (Appendix A).

Hemorrhagic stroke. Data from the National Hospital Ambulatory Medical Care Survey revealed that BP elevations occur in >60% of patients after a stroke, with the greatest elevations of SBP (≥2200 mm Hg) seen in patients with intracerebral hemorrhage (ICH). The most acute concern after ICH is hematoma volume expansion, which increases morbidity and mortality. Hematoma expansion occurs very early (first 3 hours), with limited expansion beyond 24 hours. While there is a correlation between elevated SBP (≥160 mm Hg) and hematoma volume expansion, there is no current evidence that lowering BP affects hematoma volume expansion. Aggressive BP lowering could also decrease cerebral perfusion and worsen ischemia. However, preclinical and clinical studies do not suggest the presence of a perihematomal area of hypoperfusion. One study of patients with small to medium ICH (1–45 mL) receiving i.v. nicardipine or labetalol to reduce MAP by 15% from baseline during the first 6–22 hours after ictus found that cerebral blood flow and autoregulation were preserved in the perihematomal area.

At the present time, data from few trials exist to guide BP management in patients with ICH, though the Antihypertensive Treatment of Acute Cerebral Hemorrhage (ATACH) and the Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage (INTERACT) trials are ongoing. These studies evaluate the effect on outcomes of reducing BP to specified target levels.

There are three treatment groups in the ATACH trial. The treatment goals are to reduce and maintain SBP for 24 hours from onset of symptoms to within the groups’ target ranges: (1) 170–200 mm Hg, (2) 140–170 mm Hg, and (3) 110–140 mm Hg, respectively. Nicardipine hydrochloride will be administered by continuous infusion starting at 5 mg/hr, with increases of 2.5 mg/hr as needed every 15 minutes to a maximum of 15 mg/hr. When the target dosage is reached, the infusion will be decreased to 3 mg/hr. If the BP decreases below the specified target level, the infusion should be reduced by 2.5 mg/hr every 15 minutes until discontinued.

The INTERACT study randomized patients with spontaneous ICH and elevated SBP (150–220 mm Hg) to receive either an early, intensive BP-lowering therapy or a standard strategy based on the 1999 guidelines of the American Heart Association. In the intensive group, the target SBP was 140 mm Hg within 1 hour of randomization, maintained for seven days. Treatment was discontinued if SBP decreased to 130 mm Hg. A stepped i.v. protocol was established for each institution based on what agents were available. For the guideline group, the target SBP was 180 mm Hg. Eligible patients were able to begin treatment within 6 hours of ICH onset. Results of the run-in phase of INTERACT were recently published. Baseline patient characteristics were similar, except baseline hematoma volumes were smaller in the guideline group. Mean SBP levels 1 hour after randomization were 153 mm Hg in the intensive group and 167 mm Hg in the guideline group. From 1 to 24 hours after randomization, the mean SBP levels were 146 mm Hg in the intensive group and 157 mm Hg in the guideline group. The most commonly used agents for BP lowering in this study were furosemide, urapidil, and phenolamine. Mean hematoma growth was 22.6% lower in the intensive group (95% CI, −0.6 to −44.5; p = 0.06) compared with the guideline group (13.7% versus 36.3%, respectively) after adjusting for initial hematoma volume and time from ICH to computed tomography (CT) scan. The absolute risk reduction in “substantial” hematoma growth (>33% or 12.5 mL) was 8% (95% CI, −1 to 17; p = 0.05) in the intensively managed group (15% versus 23%, respectively), equating to a relative risk reduction of 36%. The authors concluded that drug treatment to lower elevated BP can be given quickly and safely to patients with ICH. The authors also pointed out that the mean absolute difference in hematoma volume between the treatment and control groups (1.7 mL) was much smaller than in a trial of recombinant activated factor VII (4 mL), which may have been due to the shorter time between onset and treatment (4 hours). No relationship between time to treatment and efficacy was found in the INTERACT study, but this may have been due to the small sample size.

In a smaller study, two groups of patients with ICH (n = 21 per group) were randomized to standard or aggressive BP lowering (MAP = 110–130 mm Hg or <110 mm Hg).
Hg, respectively) within 8 hours of symptom onset.\textsuperscript{134} MAP was managed during the 48-hour treatment period. Standard BP-lowering agents were used, but agent selection was not strictly standardized and was done according to routine clinical practice. Typical initial treatment was intermittent labetalol hydrochloride infusions of 10–20 mg. If labetalol failed to achieve the target BP, continuous infusions of nicardipine hydrochloride 5–15 mg/hr were started. I.V. nicardipine was the initial treatment for more severe cases, with an initial dosage of 5 mg/hr titrated with increases of 2.5 mg/hr every 5–15 minutes. No bolus dose was administered. The most severe cases of hypertension were given sodium nitroprusside infusions at 0.3 μg/kg/min and adjusted every few minutes. National Institutes of Health Stroke Scale (NIHSS) scores were obtained at baseline, 24, and 48 hours. Brain CT was done 24 hours after symptom onset. A modified Rankin scale score was obtained at 90 days. A clinical decline (decrease in NIHSS score of ≥2 points) within the first 48 hours was the primary endpoint. Hematoma enlargement at 24 hours was the secondary endpoint. Treatment was started a mean ± S.D. of 3.2 ± 2.2 hours after symptom onset. Baseline clinical variables were identical between treatment groups. The target BP was achieved within a mean ± S.D. of 87.1 ± 59.6 minutes in the standard group and 163.5 ± 163.8 minutes in the aggressive-treatment group. There were no significant differences in early neurologic deterioration, hematoma and edema growth, or clinical outcomes at 90 days.

Treatment guidelines for spontaneous ICH from the Stroke Council of the American Heart Association (AHA) are listed in Appendices B and C.\textsuperscript{120} Aggressive BP reduction with continuous infusion agents is suggested for patients with an SBP of >200 mm Hg or an MAP of >150 mm Hg. Patients with an SBP of >180 mm Hg or an MAP of >130 mm Hg may receive i.v. antihypertensives, but BP reduction should be modest (e.g., MAP of 110 mm Hg or target BP of 160/90 mm Hg) and careful attention paid to maintain a cerebral perfusion pressure of >60–80 mm Hg if there is evidence of elevated ICP.\textsuperscript{120}

Qureshi et al.\textsuperscript{135} evaluated the tolerability (defined as the ability to achieve BP reduction and maintain goal MAP for 24 hours without adverse effects requiring drug discontinuation) of i.v. nicardipine for the treatment of acute hypertension (MAP of >130 mm Hg) in patients with ICH. Of the 29 patients enrolled, tolerability was achieved in 25 (86%). Neurologic deterioration occurred in 4 (14%) of the 29 patients, but no temporal relationship between BP reduction and neurologic deterioration was observed. Hematoma expansion was reported in 5 of 29 patients. Eleven patients (38%) had a modified Rankin scale score of ≤2 (independent functional status) at one month. The study investigators concluded that i.v. nicardipine achieved AHA-recommended MAP goals and was well tolerated and that the rates of hematoma enlargement and neurologic deterioration were not higher than the expected rates.

Qureshi et al.\textsuperscript{136} also evaluated the feasibility and safety of aggressive antihypertensive treatment (hydrazine and labetalol) in 27 patients with ICH. SBP was maintained below 160 mm Hg and DBP below 90 mm Hg within 24 hours of symptom onset. Neurologic deterioration was observed in 2 patients (7.4%). Of the 22 patients who underwent follow-up CT, 2 (9.1%) had hematoma expansion (more than 33% increase in hematoma size at 24 hours). The authors concluded that early aggressive pharmacologic treatment of acute hypertension in patients with ICH can be initiated early with low rates of neurologic deterioration and hematoma expansion.

Liu-DeRyke et al.\textsuperscript{137} compared treatment with labetalol (n = 64) and nicardipine (n = 26) in patients with subarachnoid hemorrhage (22%), ICH (54%), and AIS (23%). Acute Physiology and Chronic Health Evaluation (APACHE) II and Glasgow Coma Scale values were similar between groups. Initial BP levels were similar between treatment groups. Overall, the nicardipine-treated group had less BP variability (8.19 mm Hg versus 10.78 mm Hg, p = 0.003, respectively), had fewer dosage adjustments (2 versus 4, p < 0.001), and required fewer additional antihypertensive agents (8% versus 33%, p = 0.013) during the 24-hour observation period. Within the first 60 minutes of treatment in patients with ICH, 33% of the nicardipine-treated patients and 6% of the labetalol-treated group achieved target BP levels (p = 0.02). The overall prevalence of hypotension (SBP of <90 mm Hg) (labetalol, 3%; nicardipine, 0%) and bradycardia (heart rate of <60 beats/min) (labetalol, 20.6%; nicardipine, 12%) was comparable. As an alternative to labetalol, nicardipine may offer smoother BP control with comparable efficacy.

**Perioperative hypertension.**

Well-controlled perioperative BP in patients with stage 1 or 2 hypertension is not accompanied by increased cardiovascular risk during or immediately after surgery.\textsuperscript{138} However, an SBP of ≥180 mm Hg or a DBP of ≥110 mm Hg is a risk factor for perioperative ischemic events, and BP should be controlled before surgery. Rapid-acting agents can be administered preoperatively to achieve appropriate levels of BP control.

**Perioperative hypertension** (an SBP of ≥160 mm Hg or a DBP of ≥90 mm Hg or an SBP elevation of ≥20% of the preoperative value that persists for over 15 minutes) affects the patients in the operating room, postanesthesia care unit, and ICU and is associated with adverse outcomes. Postoperatively, hypertension...
Intravenous antihypertensive therapy

may be from rapid shifts in blood volume and increased sympathetic nervous system activity that accompany surgery; thus, the elevated BP may be transient in nature. Increased sympathetic tone increases vasoconstriction, vascular resistance, SBP, and DBP. Acute increases in BP in the perioperative period may increase the risk of venous or arterial hemorrhage and contribute to complications such as vascular injury, edema, hematoma, stroke, encephalopathy, arrhythmia, myocardial ischemia, renal failure, and heart failure.

Acute aortic dissection, hypertension of pregnancy, and pheochromocytoma are preoperative hypertensive emergencies, requiring aggressive lowering of BP levels before and during surgical resolution. Intraoperatively, hypertension is most frequently seen during induction of anesthesia and manipulation and intubation of the airway. Hypertension during emergence from anesthesia and extubation of the airway is another critical period for controlling BP. Operative procedures where BP manipulation becomes critical in avoiding intravascular shear stresses include peripheral vascular bypass, coronary artery bypass, carotid endarterectomy, intracranial tumor resection, and aneurysm-clipping procedures.

I.V. nicardipine has been compared with sodium nitroprusside for hypertensive therapy after coronary artery bypass graft (CABG) surgery. In 47 post-CABG patients with an SBP of $\geq 150$ mm Hg within six hours after surgery randomized to receive either i.v. nicardipine or sodium nitroprusside, both drugs were infused at 2 $\mu$g/kg/min for 10 minutes. The dosage was increased by 1 $\mu$g/kg/min every 10 minutes if the BP remained higher than the target BP and was decreased by 1 $\mu$g/kg/min when the target BP was achieved. No differences in SBP or heart rate were reported, but the duration of drug therapy and the total dose administered were lower for the nicardipine group compared with the sodium nitroprusside group. Cardiac index and stroke volume were higher and systemic vascular resistance (SVR) was lower in patients treated with nicardipine.

In another trial of 40 adult cardiac surgery patients, bolus doses of nicardipine (0.25, 0.50, 1, and 2 mg) selectively decreased arterial pressure in a dose-dependent manner, with a maximum response occurring within 100 seconds and recovery to half-maximum response in three to seven minutes without changes in heart rate. Arterial pressure decreases were associated with small decreases in left ventricular end-systolic wall stress and small increases in global left ventricular systolic function, but no effects on ventricular preload or cardiac output were noted. The absence of dose-dependent changes in cardiac output, left ventricular systolic performance, and left ventricular afterload, despite significant decreases in arterial pressure, suggested that nicardipine had a small negative inotropic action.

Postoperative hypertension is a common complication of carotid endarterectomy. I.V. nicardipine was compared with sodium nitroprusside in a randomized, double-blind trial of 60 patients requiring antihypertensive treatment after carotid endarterectomy. Patients randomized to nicardipine required a shorter time to achieve the target BP level (83% nicardipine versus 23% sodium nitroprusside within the first 10 minutes, $p < 0.01$). Nicardipine was associated with less BP variability compared with sodium nitroprusside. More patients receiving sodium nitroprusside required additional dosage adjustments to maintain BP within the goal range. The rates of adverse events did not significantly differ between groups, although the study was not powered to evaluate clinical outcomes such as death, myocardial ischemia, and stroke.

Clevidipine has been compared with sodium nitroprusside for the treatment of hypertension after CABG, with SVR and heart rate found to be lower with clevidipine while preload, stroke volume, and pulmonary vascular resistance were higher with clevidipine versus sodium nitroprusside. There were no differences in myocardial lactate metabolism or oxygen extraction with clevidipine versus sodium nitroprusside. A postcardiac surgery clevidipine dose-ranging trial found significant decreases in MAP and systemic vascular resistance at doses of $\geq 1.37 \mu$g/kg/min ($p < 0.05$). No changes in heart rate, central venous pressure, pulmonary artery occlusion pressure, or cardiac index were found with increasing doses of clevidipine. During 12 hours of infusion, clevidipine decreased SVR and MAP without changing heart rate, cardiac index, or cardiac filling pressures, and the half-life remained less than two minutes.

Levy et al. studied clevidipine’s efficacy in the management of preoperative hypertension (SBP of $\geq 160$ mm Hg) in awake patients before cardiac surgery. Of the 53 patients treated with clevidipine, 49 (92.5%) achieved treatment success ($\geq 15%$ reduction in SBP) and 4 (7.5%) had a significantly lower rate of treatment failure than patients receiving placebo (82.7% [43 of 52], $p < 0.0001$). Target BPs were achieved at a median of 6.0 minutes (95% CI, 6–8 minutes) with clevidipine, with a modest increase in heart rate from baseline. The rates of adverse events were similar between treatment groups.

Data reported from double-blind, placebo-controlled trials evaluated the ability of clevidipine to control BP in high-risk cardiovascular surgery patients. In both trials, clevidipine-treated patients demonstrated a significant decrease in MAP ($p < 0.0001$) compared with placebo at 5 minutes. A BP-lowering effect was observed within 1–2 minutes.
with clevidipine, and the median times to achieve the target SBP in the two studies were 6 and 5.3 minutes.\textsuperscript{143} Two of the 100 patients receiving clevidipine discontinued therapy before the end of the 30-minute treatment period because of a too-rapid decline in SBP (from 140 to 100 mm Hg in \textsuperscript{=}3 minutes and from 140 to 108 mm Hg in \textsuperscript{=}3 minutes).\textsuperscript{144}

In the Evaluation of Clevidipine in the Perioperative Treatment of Hypertension Assessing Safety Events (ECLIPSE) trials (three prospective, randomized, open-label, parallel comparison studies) the safety and efficacy of clevidipine to nitroglycerin or sodium nitroprusside perioperatively or to nicardipine postoperatively or sodium nitroprusside perioperatively or to nicardipine postoperatively were analyzed in 1512 patients with perioperative acute hypertension undergoing cardiac surgery.\textsuperscript{145} Clevidipine was given using a pre-specified dosing regimen, while the comparator drugs were given based on individual institutional practices. No difference in the incidence of MI, stroke, or renal dysfunction was found for clevidipine versus any of the comparators. However, 30-day mortality was significantly higher in patients who received sodium nitroprusside versus clevidipine, but no differences in mortality were seen when clevidipine was compared with nitroglycerin or nicardipine. For the secondary endpoint, clevidipine was more effective than sodium nitroprusside (\textit{p} = 0.003) and nitroglycerin (\textit{p} = 0.003) in maintaining BP in the prespecified BP range (SBP of 75–146 mm Hg) but was equivalent to nicardipine. The frequency of serious adverse events was similar among treatment groups.

\textbf{Acute aortic dissection.} In order to avoid progressive intimal dissection, acute aortic dissection requires immediate i.v. antihypertensive treatment (except in hypotensive patients) as soon as the diagnosis is suspected.\textsuperscript{7} Emergency treatment typically involves rapid i.v. \textit{\beta}-blockade with esmolol and may include a vaso-dilator such as nicardipine or sodium nitroprusside to achieve an SBP of \\textless{}120 mm Hg within 20 minutes.\textsuperscript{146} It is important that \textit{\beta}-blockade precedes the administration of any drug that may cause reflex tachycardia or a reflex positive inotropic effect, as this may exacerbate the dissection. This BP level should be maintained for as long as it is tolerated or until intraoperative control of the aorta is accomplished.

Although esmolol is approved only for use in perioperative settings, it has been used to treat hypertension associated with acute aortic dissection, repair of coarctation, and pheochromocytoma and during or after cardiac surgery and neurosurgery. It has also been used in patients with relative contraindications to \textit{\beta}-blocker therapy\textsuperscript{77,21,75} and it lowers BP to a degree comparable to that achieved with sodium nitroprusside.\textsuperscript{73}

\textbf{Preeclampsia and eclampsia.} No specific antihypertensive agent is recommended by FDA in pregnancy; however, ACE inhibitors and sodium nitroprusside are contraindicated. Historically, hydralazine has been considered the first-line antihypertensive treatment for preeclampsia and eclampsia.\textsuperscript{1} It crosses the placenta, but not to a significant degree, and does not decrease placental blood flow.\textsuperscript{147} I.V. hydralazine is generally well tolerated, although it is associated with reflex tachycardia, headache, angina, flushing, nausea, and vomiting.\textsuperscript{1} Although long-term administration of oral hydralazine is linked to the development of a lupuslike syndrome, this is not expected to occur with short-term i.v. administration. Hydralazine’s unpredictability of response and prolonged duration of action are of concern in these patients.\textsuperscript{23}

Labetalol also has been used effectively in managing hypertension during pregnancy.\textsuperscript{104,148-151} There is little placental transfer, due mainly to the drug’s negligible lipid solubility.\textsuperscript{7} In a study of 200 pregnant patients randomized to receive labetalol hydrochloride (20-mg i.v. bolus dose followed by 40 mg if not effective within 20 minutes, followed by 80 mg every 20 minutes up to a maximum dose of 300 mg) or hydralazine hydrochloride (5 mg as a slow i.v. bolus dose and repeated every 20 minutes up to a maximum of five doses), no significant differences were observed in the rates of maternal hypotension.\textsuperscript{152} Only 2 patients in the hydralazine-treated group developed hypotension, while palpitations (\textit{p} = 0.01) and maternal tachycardia (\textit{p} = 0.05) occurred significantly more often in patients treated with hydralazine versus labetalol. The main outcomes in neonates were very similar per group; however, hypotension (\textit{p} = 0.05) and bradycardia (\textit{p} = 0.008) were more frequent in the labetalol group. There were two neonate deaths in each treatment group. Both labetalol and hydralazine were felt to fulfill the criteria required for an antihypertensive drug to treat severe hypertension in pregnancy.\textsuperscript{152}

I.V. nicardipine was compared to labetalol for the treatment of hypertensive emergency in pregnancy.\textsuperscript{148} In a study of 60 women beyond 24 weeks of gestation, both i.v. nicardipine and labetalol effectively lowered BP by at least 20% from baseline (70% versus 63%, respectively; \textit{p} = 0.58). The time to achieve the target BP was similar between groups. No hypertensive episodes occurred in either group, and both drugs were well tolerated.

\textbf{Acute coronary syndromes.} Nitroglycerin reduces preload and decreases myocardial oxygen consumption by decreasing left ventricular end-diastolic volume and myocardial wall tension.\textsuperscript{7,66} This makes nitroglycerin the preferred agent in the setting of hypertensive emergencies complicated by myocardial ischemia.\textsuperscript{1} However, before the administration of any vasoactive nitrate, physicians and paramedics should inquire about the use of phosphodiesterase-5 (PDE5) inhibitors. Nitrates given in...
the presence of a PDE5 inhibitor can cause profound hypotension for up to 48 hours after the last dose of a PDE5 inhibitor. In one study, standing SBP fell below 85 mm Hg in more patients receiving tadalafil compared with placebo (p < 0.05), with no difference in the response to sublingual nitroglycerin after 48, 72, and 96 hours.155

Within 48 hours after the last dose of a PDE5 inhibitor, ischemic chest pain can be treated with β-blockers, CCBs, morphine, oxygen, and aspirin; nitrates should be avoided. In patients with an acute MI within 48 hours of tadalafil administration, there is no contraindication to using usual therapy such as aspirin, heparin, percutaneous coronary intervention, or thrombolytics, but nitrates should not be given.155

A meta-analysis of pre fibrinolytic era trials involving more than 24,000 patients receiving β-blockers found a 14% risk reduction in mortality through seven days and a 23% reduction in long-term mortality.154 Inhospital β-blockers reduce infarct size and rates of mortality, postinfarction ischemia, and nonfatal acute MI. I.V. β-blockers may also be beneficial for non-ST-segment elevation MI acute coronary syndrome.66 The Clopidogrel and Metoprolol in Myocardial Infarction Trial (COMPETE) of 45,852 patients randomized to receive early treatment with i.v. metoprolol or placebo found that while early i.v. β-blocker therapy in acute MI reduced the risks of reinfarction and ventricular fibrillation, it increased the risk of cardiogenic shock, especially within 24 hours after admission.155 Although oral β-blocker therapy is still recommended, the authors cautioned prudence in starting i.v. β-blocker therapy, which should be used in the hospital only after the post-MI hemodynamic status has stabilized. Contraindications to β-blockers are moderate-to-severe left ventricular failure with pulmonary edema, bradycardia (<60 beats/min), hypotension (SBP of <100 mm Hg), poor peripheral perfusion, second- or third-degree heart block, and reactive airways disease.66

Enalaprilat may be a favorable option in patients with hypertensive emergency in the setting of left ventricular failure,1 since ACE inhibitors are a cornerstone treatment in heart failure. In contrast, the Cooperative New Scandinavian Enalapril Survival Study II (CONSENSUS II) showed a trend toward increased mortality when enalaprilat was administered within 24 hours of acute MI, an observation that may have been due to hypotension after drug administration.1,156

APE. Because dyspnea, anxiety, or chest pain accompanies APE, nearly 50% of patients with APE are hypertensive (SBP of >140 mm Hg). Supplemental oxygen, afterload and preload reductions, and diuresis are the primary therapeutic goals in the treatment of APE. BP reduction will reduce myocardial oxygen demand and may enhance cardiac output. Immediate BP reduction is necessary with acute APE. Nitroglycerin, sodium nitroprusside, and nesiritide are the three i.v. antihypertensives most commonly used to treat APE.64

In one study, high-dose nitroglycerin was used to aggressively lower BP in 29 patients (SBP of ≥160 mm Hg or MAP of ≥120 mm Hg and APE) with severe decompensated heart failure refractory to initial antihypertensive therapy.157 This single-group, nonrandomized, open-label, standard therapy controlled study evaluated high-dose boluses of nitroglycerin (2 mg i.v. every three minutes up to 10 doses) adjusted to symptomatic response. In the high-dose nitroglycerin group, fewer ICU admissions (37.9% versus 80.0%), fewer endotracheal intubations (13.8% versus 26.7%), and fewer troponin-level elevations (17.2% versus 28.9%) occurred compared with standard therapy. One patient treated with high-dose nitroglycerin developed symptomatic hypotension (3.4%). The mean ± S.D. nitroglycerin dose was 6.5 ± 3.4 mg. None of the 45 patients treated with standard therapy developed symptomatic hypotension; however, 28.9% had biomarker evidence of MI. This is a special case of treatment where rapid BP declines in patients with acute severe pulmonary congestion, exceeding those recommended by the JNC-7, may result in the avoidance of endotracheal intubation.157

I.V. nesiritide was compared with i.v. nitroglycerin in the Vasodilata -tion in the Management of Acute CHF (VMAC) study of 489 patients with dyspnea at rest from decompensated congestive heart failure.90 All patients received baseline standard therapy as needed (e.g., loop diuretics, dobutamine or dopamine, antiarrhythmics, or i.v. vasoactive medications) and were randomized to receive nitroglycerin, nesiritide, or standard care. Nesiritide reduced pulmonary capillary wedge pressure to a significantly greater extent than did nitroglycerin or placebo at all time points (15, 60, and 180 minutes) (p < 0.05 for active therapy versus placebo and for nesiritide versus nitroglycerin at all time points). The rates of symptomatic hypotension were similar for patients treated with either nitroglycerin or nesiritide (5% versus 4%). Overall, adverse events occurred in 18% of nesiritide-treated patients, 27% in patients treated with nitroglycerin and 14% in placebo-treated patients (p = 0.02). Headache was the most common adverse effect, occurring in 12% of the nitroglycerin group, 5% of the nesiritide group, and 2% of the patients receiving placebo (p = 0.003).90

Conclusion

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

References

134. Qureshi AI, Harris-Lane P, Kirmani JF et al. Treatment of acute hypertension


Appendix A—Guideline-based recommendations for managing arterial hypertension in acute ischemic stroke

A. Indications that patient is eligible for treatment with i.v. recombinant tissue plasminogen activator (rt-PA) or other acute reperfusion intervention

1. If systolic blood pressure (SBP) is >185 mm Hg or diastolic blood pressure (DBP) is >110 mm Hg, use a. Labetalol 10–20 mg i.v. over 1–2 minutes, may repeat once or b. Nitropaste 1–2 inches or c. Nicardipine 5–mg/hr infusion, increase dosage by 2.5 mg/hr every 5–15 minutes to a maximum dosage of 15 mg/hr; when desired blood pressure (BP) attained, reduce dosage to 3 mg/hr

2. If BP does not decline and remains >185/110 mm Hg, do not administer rt-PA

B. Managing BP during and after treatment with rt-PA or other acute reperfusion intervention: Monitor BP every 15 minutes during treatment and then for another 2 hours, then every 30 minutes for 6 hours, and then every hour for 16 hours

1. If SBP is 180–230 mm Hg or DBP is 105–120 mm Hg, use a. Labetalol 10 mg i.v. over 1–2 minutes, may repeat every 10–20 minutes to a maximum dose of 300 mg or b. Labetalol 10 mg i.v. followed by an infusion of labetalol 2–8 mg/min

2. If SBP is >230 mm Hg or DBP is 121–140 mm Hg, use a. Labetalol 10 mg i.v. over 1–2 minutes, may repeat every 10–20 minutes to a maximum dose of 300 mg or b. Labetalol 10 mg i.v. followed by an infusion of labetalol 2–8 mg/min or c. Nicardipine 5–mg/hr infusion, increase dosage by 2.5 mg/hr every 5 minutes to a maximum of 15 mg/hr until desired effect is achieved

3. If BP is still not controlled, consider sodium nitroprusside
Appendix B—Guideline-based recommendations for treating elevated blood pressure in spontaneous intracerebral hemorrhage

1. If systolic blood pressure (SBP) is >200 mm Hg or mean arterial pressure (MAP) is >150 mm Hg, consider aggressive reduction of blood pressure (BP) with continuous i.v. infusion with frequent BP monitoring every 5 minutes.

2. If SBP is >180 mm Hg or MAP is >130 mm Hg and there is evidence or suspicion of elevated intracranial pressure (ICP), consider monitoring ICP and reducing BP using intermittent or continuous i.v. medications to keep cerebral perfusion pressure at >60–80 mm Hg.

3. If SBP is >180 mm Hg or MAP is >130 mm Hg and there is no evidence or suspicion of elevated ICP, consider a modest reduction of BP (e.g., MAP of 110 mm Hg or target BP of 160/90 mm Hg) using intermittent or continuous i.v. medications to control BP and clinically reexamine the patient every 15 minutes.

Appendix C—I.V. antihypertensives for treating elevated blood pressure in patients with intracerebral hemorrhage

<table>
<thead>
<tr>
<th>Drug</th>
<th>I.V. Bolus Dose</th>
<th>Continuous Infusion Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enalapril</td>
<td>1.25–5 mg i.v. push every 6 hr*</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Esmolol</td>
<td>250 µg/kg i.v. push loading dose</td>
<td>25–300 µg/kg/min</td>
</tr>
<tr>
<td>Hydralazine</td>
<td>5–20 mg i.v. push every 30 min</td>
<td>1.5–5 µg/kg/min</td>
</tr>
<tr>
<td>Labetalol</td>
<td>5–20 mg every 15 min</td>
<td>2 mg/min (maximum of 300 mg daily)</td>
</tr>
<tr>
<td>Nicardipine</td>
<td>Not applicable</td>
<td>5–15 mg/hr</td>
</tr>
<tr>
<td>Nitroglycerin</td>
<td>Not applicable</td>
<td>20–400 µg/min</td>
</tr>
<tr>
<td>Nitroprusside</td>
<td>Not applicable</td>
<td>0.1–10 µg/kg/min</td>
</tr>
</tbody>
</table>

*Because of the risk of precipitous blood pressure lowering, the enalapril first test dose should be 0.625 mg.