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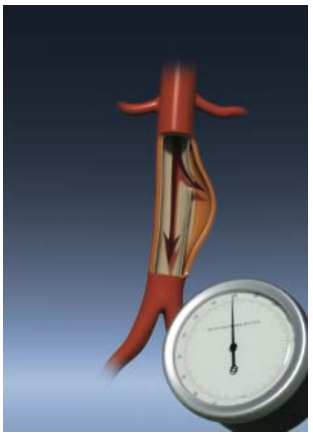

Recent Advances in the Treatment of Hypertensive Emergencies

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PRIME POINTS

- This review defines hypertensive crisis, hypertensive urgencies, and hypertensive emergencies and provides recent updates on the management of acute hypertension.
- Nurses are immediately involved in the care of patients with hypertensive emergencies and must know the appropriate treatment for these patients.
- Currently available intravenous antihypertensive medications, recommended doses, common adverse effects, and compatibilities are discussed in this paper.

Approximately 73.6 million people in the United States aged 20 years or older are affected by hypertension.[1] Although significant improvements have been made with regard to awareness and treatment of hypertension, approximately 30% of adults are still unaware of their disease.[2] Up to 40% of people with hypertension are not receiving treatment, and up to 67% of those treated are not achieving blood pressure control.[2] Hypertension is one of the most common chronic medical conditions, and it occurs almost twice as frequently in African Americans as in whites.[3] The rate is slightly higher in women than in men, and the incidence increases with age.[4,5]

In its seventh report, the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure provided categorical definitions of hypertension, which are presented in Table 1.[2] A hypertensive crisis is defined as an acute elevation of blood pressure, with a systolic pressure greater than 180 mm Hg or a diastolic pressure greater than 110 mm Hg.[6] It is estimated that 1% of patients with hypertension will have a hypertensive crisis.[7] When evidence of acute or ongoing damage of a target organ is present, the condition is considered a hypertensive emergency and the rapid reduction of blood pressure is indicated.[6] Clinical findings of target

CE Continuing Education

This article has been designated for CE credit. A closed-book, multiple-choice examination follows this article, which tests your knowledge of the following objectives:

1. Define hypertensive crisis
2. Describe the initial goal of treatment in hypertensive emergencies
3. Discuss the mechanism of action, onset of action, duration of action, adverse effects, dosage, and administration of clevidipine

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Table 1 Categorical definitions of hypertension[a]

Blood pressure	Blood pressure, mm Hg	
	Systolic	Diastolic
Normal	<120	and <80
Prehypertension	120-139	or 80-89
Stage 1	140-159	or 90-99
Stage 2	≥160	or ≥100
Hypertensive urgency	>180	>110
Hypertensive emergency	>180	>110 plus end-organ damage

[a] Based on data from Chobanian at el.[2]

organ damage include, but are not limited to, hypertensive encephalopathy, intracranial hemorrhage, unstable angina, acute myocardial infarction, acute left ventricular failure with pulmonary edema, aortic dissection, and eclampsia.[8] If no evidence of end-organ damage is present, the hypertensive crisis is considered a hypertensive urgency and can be treated less aggressively. In this update, we focus on hypertensive emergencies.

At this point, no national guidelines have been developed for the treatment of acute hypertension, including hypertensive emergencies, except for patients who have had an ischemic stroke, aortic dissection, or eclampsia.[9-11] However, the pharmacotherapy and management principles are important to critical care nurses because this condition requires immediate detection and treatment to prevent or minimize target end-organ damage. In August 2008, clevidipine received approval from the Food and Drug Administration (FDA) for use in treating hypertensive emergencies in the United States.[12-17] This newly approved drug is the first in several years to be approved by the FDA to treat hypertensive emergencies. The purpose of this article is to provide critical care nurses with recent updates on the management of this acute disease.

Pathophysiology

The pathophysiology of hypertensive emergencies is not well understood. It is postulated that failure of autoregulation and an abrupt increase in systemic vascular resistance (SVR) are initial steps in the disease process.[18] Increases in SVR are thought to occur after the release of vasoconstrictors from the wall of a stressed vessel.[19] The increased pressure within the vessel then starts a cycle of endothelial damage, activation of the clotting cascade, fibrinoid necrosis of small blood vessels, and the release of more vasoconstrictors.[19] If the process is not stopped, the cycle of further vascular injury, tissue ischemia, and autoregulatory dysfunction continues.[7] Most patients with a hypertensive emergency have uncontrolled hypertension or have recently discontinued their medications.[19] Thus, a thorough medical and medication history collected by the critical care nurse can provide valuable information and assist in the successful treatment of the hypertensive emergency.

Treatment

The treatment of hypertensive emergencies is based on the rapid, controlled reduction of blood pressure without the development of hypotension. Management of this syndrome is based on expert consensus and not on evidence-based literature because of the lack of large clinical trials on this topic.[6,7,19,20] Upon initial presentation, patients with hypertensive emergencies should be admitted to an intensive care unit (ICU) and may have an arterial catheter placed to facilitate frequent and accurate cardiac monitoring.[19] Markers of progressive organ damage

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such as serum level of creatinine, urine output, electrocardiography results, hemodynamic monitoring, findings on chest radiographs, patient's neurological status, and findings on ocular examinations should be assessed frequently.[7]

The initial goal of treatment is to reduce the mean arterial pressure by no more than 25% to reach a goal blood pressure of 160/100 mm Hg within 2 to 6 hours or to decrease diastolic blood pressure 10% to 15% or to approximately 110 mm Hg within 30 to 60 minutes.[6,7,21] It is important that blood pressure be lowered in a controlled manner to avoid risk for hypoperfusion of vital organs, which can cause ischemia and infarction.[7] To ensure controlled lowering of blood pressure, critical care nurses should monitor blood pressure every 5 to 10 minutes until goals are reached.

When choosing pharmacological therapy, fast-acting, intravenous, easily titratable antihypertensive medications are generally used. A specific agent is then chosen on the basis of the type of end-organ damage that is present and should be used in an ICU setting to minimize abrupt decreases in blood pressure. The preferred agents include labetalol, esmolol, nitroglycerin, nicardipine, fenoldopam, and sodium nitroprusside.[21] Clevidipine, an intravenous calcium channel blocker, was approved by the FDA in August 2008 for the management of acute, severe hypertension after it demonstrated safety and efficacy in clinical trials.[12-17] The common doses and adverse effects of the medications used to treat hypertensive emergencies are listed in Table 2.

Labetalol, an intravenous nonselective β-blocker that also possesses α_1-blocking effects, is an agent that is commonly used to treat hypertensive emergencies. It produces its

Table 2 Dosage, adverse effects, and recommended disease states[a]

Medication	Administration	Onset of action, min	Duration of action	Adverse effect
Clevidipine	Initial infusion of 1-2 mg/h, can increase dose every 5-10 minutes	2-4	5-15 min	Headache, nausea, vomiting, hypotension, rebound hypertension, reflex tachycardia
Esmolol	0.5 mg/kg initial dose Infusion of 25-300 μg/kg per minute	1	10-20 min	Nausea, flushing, first-degree heart block, bronchospasm
Fenoldopam	0.1 μg/kg per minute starting infusion	5	30-60 min	Nausea, headache, flushing
Labetalol	Loading dose of 20 mg Infusion of 1-2 mg/min and titrate to effect or repeat doses of 20-80 mg at 10-min intervals	2-5	2-4 h	Hypotension, dizziness, bronchospasm, nausea, vomiting
Nicardipine	Infusion of 5 mg/h increasing by 2.5 mg/h every 5 min (maximum, 15 mg/h)	5-15	4-6 h	Headache, dizziness, flushing, edema, tachycardia
Nitroglycerin	5 μg/min, increase by 5 μg/min every 3-5 minutes up to 20 μg/min If no response at 20 μg/min, increase by 10 μg/min every 3-5 min, up to 200 μg/min	1-5	5-10 min	Reflex tachycardia, tachylplylaxis, hypoxemia
Sodium nitroprusside	Initial 0.3-0.5 μg/kg per minute Increase in increments of 0.5 μg/kg per minute (maximum 2 μg/kg per minute to avoid toxic effects)	Within seconds	1-2 min	Toxic effects of thiocyanate and cyanide, headache, muscle spasm, flushing

[a] Based on data from Marik and Varon,[21] Varon and Marik,[22] Mayne Pharma,[23] Pearce and Wallin,[24] Baxter Healthcare,[25] Abbott Laboratories,[26] and Gahart and Nazareno.[27]
[b] Abbreviations: D5W, dextrose 5%; D5WLR, dextrose 5% with lactated Ringer solution; D5WNS, dextrose 5% with normal saline; LR, lactated Ringer solution; NS, normal saline; SW, sterile water; 1/2NS, half normal saline.
[c] Associated with diastolic dysfunction.
[d] In combination with intravenous nitroglycerin.
[e] Associated with systolic dysfunction.

antihypertensive effect by decreasing the heart rate and lowering SVR.[22] This medication can be given as an intravenous bolus or as a continuous infusion. The hypotensive effects of labetalol begin within 2 to 5 minutes after an intravenous bolus and peak at 5 to 15 minutes. The effects can last for 2 to 4 hours.[23] Because this medication does not have pure β-blocking effects, the patient's cardiac output is maintained. Labetalol does reduce peripheral vascular resistance because of its α-blocking effects, and it does not reduce peripheral blood flow.[24] This medication is best used when the following conditions are present: acute myocardial ischemia, aortic dissection, acute postoperative hypertension, acute ischemic stroke, hypertensive encephalopathy, preeclampsia, and eclampsia.[21]

Clinicians should be aware of the possible adverse effects associated with labetalol, especially the development of sinoatrial/atrioventricular nodal dysfunction, such as heart block. Extra consideration must also be taken for patients with a history of restrictive airway disease, such as asthma, because of the possible development of bronchospasm. Bronchospasm may result from the nonselective β-receptor blockade properties of labetalol.

Esmolol, an intravenous, cardioselective β-blocker, has a rapid onset and a short duration of action, which makes it easy to titrate its dosage. This medication lowers blood pressure through a decrease in atrial pressure by decreasing the rate and contractility of the heart through the blockade of β_1 receptors.[19] Esmolol is given as an initial 0.5 to 1.0 mg/kg intravenous loading dose for 1 minute and is followed by a continuous infusion. It is an ideal agent for situations where the cardiac output, heart rate, and blood pressure are increased, especially when a patient is experiencing acute pulmonary edema, diastolic dysfunction, acute aortic dissection, and acute postoperative hypertension.[21] Caution should be used when this medication is given to patients with restrictive lung disease because of the possibility of bronchospasm, as seen with labetalol. The American College of Cardiology and the American

Contraindication	Compatibility[b]	Disease for which the drug is recommended
Allergy to soy or eggs, defective lipid metabolism, severe aortic stenosis	SW, NS, D5WNS, D5W, D5WLR, LR, 10% amino acids	Perioperative, postoperative, persistent severe hypertension in patients with renal dysfunction or acute heart failure
Hypersensitivity, severe bradycardia, heart block greater than first degree, cardiogenic shock, bronchial asthma, uncompensated cardiac failure	1/2 NS, NS, D5W, D5NS, D51/2NS, D5LR	Acute pulmonary edema,[c] acute myocardial ischemia,[d] acute aortic dissection, acute postoperative hypertension
Hypersensitivity to fenoldopam, hypersensitivity to sulfites	NS, D5W	Acute pulmonary edema,[e] hypertensive encephalopathy, acute renal failure, acute ischemic stroke
Hypersensitivity, severe bradycardia, heart block greater than first degree, cardiogenic shock, bronchial asthma, uncompensated cardiac failure	LR, D5W, D5WLR, NS, D5WNS	Acute pulmonary edema,[c] hypertensive encephalopathy, acute myocardial ischemia,[d] acute aortic dissection, acute postoperative hypertension, eclampsia, ischemic stroke
Advanced or preexisting aortic stenosis, hypersensitivity to nicardipine	NS, D5W, 1/2NS, D51/2NS, D5NS	Acute pulmonary edema,[e] hypertensive encephalopathy, acute renal failure, sympathetic crisis, acute ischemic stroke, acute postoperative hypertension
Concurrent use of phosphodiesterase inhibitors such as sildenafil or vardenafil, constrictive pericarditis, pericardial tamponade, restrictive cardiomyopathy, sensitivity to organic nitrates	D5W, NS	Adjunct agent for acute pulmonary edema[c-e] and acute myocardial ischemia
Compensatory shunting, congestive heart failure associated with reduced peripheral vascular resistance, hypersensitivity to nitroprusside, surgical patients with inadequate cerebral circulation, optic atrophy, tobacco amblyopia	D5W, SW	Acute pulmonary edema, acute aortic dissection

Heart Association also concluded that esmolol may be contraindicated in patients with decompensated heart failure and bradycardia.[28]

Intravenously administered nitroglycerin is a potent vasodilator, and when used in high doses, arterial tone is affected.[29] It reduces blood pressure by reducing both afterload and preload. These effects are undesirable in patients with compromised renal and cerebral perfusion.[21] It has an onset of action of 1 to 5 minutes and a duration of action of 5 to 10 minutes after the continuous infusion is discontinued.[25] Although nitroglycerin has pharmacokinetic properties similar to those of sodium nitroprusside, it is not considered a first-line agent for the treatment of hypertensive emergencies, primarily because of its side effects of reflex tachycardia and tachyphylaxis.[7] Nitroglycerine is not as efficacious as sodium nitroprusside.[7] However, it may be used as an adjunctive agent for hypertensive emergencies associated with myocardial ischemia or pulmonary edema.[21]

Nicardipine is an intravenous dihydropyridine-derivative calcium channel blocker and produces its antihypertensive effects by vasodilation of coronary vasculature and relaxation of smooth muscle.[7] This medication has high vascular selectivity and strong cerebral and coronary vasodilatory activity.[7] It has an onset of action of 5 to 15 minutes and duration of action of 4 to 6 hours. However, because of nicardipine's half-life of approximately 1 hour, titration of dosage is more difficult than with other intravenous antihypertensive medications. The dosing of this medication is independent of weight, which can be useful in most hypertensive emergencies, especially in high adrenergic states.[21]

Fenoldopam is an unique agent among the intravenous antihypertensive medications. It is a dopamine D_1-receptor agonist that was approved in 1997 for hypertensive emergencies. This medication causes peripheral vasodilation by acting upon peripheral dopamine type 1 receptors.[7] Fenoldopam also activates dopaminergic receptors on the proximal and distal tubules of the kidney, thereby inhibiting sodium reabsorption, resulting in diuresis and naturesis.[30] It has an onset of action of 5 minutes and a duration of effect of 30 to 60 minutes.

This medication improves creatinine clearance, urine flow rates, and sodium excretion in patients with and without normal kidney function.[31] It is recommended in cases of acute pulmonary edema, diastolic dysfunction, hypertensive encephalopathy, acute renal failure, and microangiopathic anemia.[21] When using this medication, clinicians should be aware of the risk for hypersensitivity reactions. Fenoldopam is in a solution that contains sodium metabisulfate, and patients with a hypersensitivity to sulfite may have an acute allergic reaction. This medication should also be avoided in patients with increased intraocular hypertension and glaucoma due to the dose-dependent increase in intraocular pressure associated with this medication.[26]

Historically, sodium nitroprusside was the drug of choice to treat hypertensive emergencies, however, because of its toxicity, it has fallen out of favor as the first-line agent.[7] This agent is a potent arterial and venous vasodilator through the generation of cyclic guanine monophosphate. These vasodilatory effects decrease both afterload and preload. Advantageous properties of this medication, and benefit of its use, are its short duration of action of 1 to 2 minutes and its half-life of 3 to 4 minutes. This property also makes the drug easy to titrate. However, abrupt cessation of the infusion results in a rapid increase in blood pressure.[22] Because of its quick onset of action, arterial blood pressure monitoring is recommended.[21] Sodium nitroprusside increases intracranial pressure, which would be disadvantageous in patients with hypertensive encephalopathy or cerebrovascular accident.[21] The use of sodium nitroprusside in patients with coronary artery disease may also result in deleterious effects because of a reduction in regional blood flow, resulting in coronary steal in such patients.[7]

Sodium nitroprusside may also lead to cyanide poisoning. It contains 44% cyanide by weight that is released nonenzymatically from sodium nitroprusside, with the amount released dependent on the dose. Infusions at rates of greater than 4 µg/kg per minute for 2 to 3 hours have led to cyanide levels within the toxic range.[32] This medication is recommended for use only in patients who have normal renal and hepatic function and when other intravenous antihypertensive medications are not available.[16] If higher infusions of sodium nitroprusside are needed, an infusion of thiosulfate should be used to prevent the accumulation of cyanide.[33]

The newest intravenous antihypertensive agent approved for hypertensive emergencies is clevidipine.

It was approved by the FDA in August 2008 and is currently available as Cleviprex (The Medicines Co, Parsippany, New Jersey), which is a racemic mixture in a lipid emulsion.[12] This medication is a third-generation dihydropyridine calcium channel blocker that inhibits L-type calcium channels in a voltage-dependent manner. The blood pressure lowering by this medication is dose dependent and rapid, with a short half life of 1 to 2 minutes, a quick onset of action of 2 to 4 minutes and a short duration of action of 5 to 15 minutes. These properties make this medication easy to titrate.[12] Clevidipine lowers systemic vascular resistance and does not affect the venous capacitance vessels or cardiac filling pressures. When compared with sodium nitroprusside, it has greater effects on arterial vasodilatation and fewer effects on venodilatation.[13]

Clevidipine is highly protein bound (>99.5%), rapidly distributed, and has a small volume of distribution. This medication is metabolized primarily by esterases that are located in the blood and extravascular tissues, to 2 inactive metabolites. The metabolites are eliminated primarily in the urine (63%-74 %) and feces (7%-22 %).[12] Although studies have not been conducted in patients with hepatic or renal impairment, the metabolism and elimination of clevidipine should not be affected by impairment of these organs.[12] Clevidipine is available as a sterile, milky, white injectable emulsion in 2 preparations: a 50-mL single-use vial with 0.5 mg/mL clevidipine butyrate or a 100-mL single-use vial with 0.5 mg/mL clevidipine butyrate. Clevidipine can be administered via a peripheral or a central catheter and should not be administered through the same catheter as other medications. The unused portion of the vial should be discarded 4 hours after the stopper is punctured. Clevidipine is contraindicated in patients with allergies to soy products, and eggs or egg products.[12] Because of the lipid emulsion preparation of clevidipine, patients receive 2 kcal per milliliter of clevidipine.[12] Patients with significant disorders of lipid metabolism may need a reduction in the quantity of the concurrently administered lipids to compensate for the lipids and kilocalories received from the clevidipine preparation.[12]

The antihypertensive efficacy of intravenous clevidipine was compared with a placebo in cardiac surgery patients in 2 randomized, double-blind multicenter studies.[14,15] These studies showed that clevidipine was effective in the treatment of both acute preoperative and postoperative hypertension.[14,15] The antihypertensive efficacy of clevidipine was also compared with the efficacies of nitroprusside, nitroglycerin, and nicardipine.[32] Overall the blood pressure control was similar among the 4 treatments.[12,16]

Clevidipine was also evaluated for use in the perioperative setting in patients with severe hypertension in the Evaluation of the Effect of Ultra-Short-Acting Clevidipine in the Treatment of Patients With Severe Hypertension (VELOCITY) study.[17] In that open-label, single-arm study, the efficacy and safety of clevidipine for treatment of severe hypertension were assessed in 126 patients who came to the emergency department or ICU with severe hypertension (defined as 2 consecutive measurements of systolic blood pressure exceeding 180 mm Hg or a measurement of diastolic blood pressure exceeding 110 mm Hg taken 15 minutes apart) with or without evidence of end-organ damage.[17] Overall, 89% of patients were able to achieve the target systolic blood pressure within 30 minutes of the time that treatment with clevidipine was started. The median time to systolic blood pressure control was 10.9 minutes (95% confidence interval: 9.0, 15.0), and more than 90% of patients maintained blood pressure control on clevidipine monotherapy without the need for additional intravenous antihypertensive therapy.[17] In that study, the most common adverse reactions occurring in more than 2% of patients included headache, nausea, and vomiting. When clevidipine is used, it should be started as a continuous intravenous infusion of 1 to 2 mg/h and titrated every 5 to 10 minutes to the desired blood pressure response.[12]

A survey of critical care physicians and pharmacists was recently conducted to evaluate which intravenous antihypertensive medications are commonly used in hypertensive emergencies and how many hospitals possess acute hypertensive guidelines. Additionally, they described the incidence of adverse effect associated with the agents used.[8] Overall 393 critical care physicians and pharmacists (7.1%) returned responses to the survey. Only 10.3 % of physicians and 4.5% of pharmacists reported

dotmore

To learn more about hypertension, read "Managing Hypertension in Patients With Stroke: Are You Prepared for Labetalol Infusion?" by Cindy Harrington in *Critical Care Nurse,* 2003;23(3):30-38. Available at **www.ccnonline.org**.

that their institution had hypertensive emergency guidelines for nonstroke patients. The agent of choice for hypertensive emergencies in nonstroke patients was intermittent intravenous labetalol among both physician and pharmacist responders.[8] However, the first- and second-line agents used varied widely. This variation may be due to the lack of national guidelines, the lack of evidence, and the need for additional education.

Summary

Clinical practice varies regarding the choice of agent to treat hypertensive emergencies.[8] With the development of national guidelines, a standardized pharmacotherapeutic approach would be recommended on the basis of evidence in the published literature. Such an approach might decrease the variability among practitioners and institutions in the treatment of hypertensive emergencies.[8]

Each available agent to treat hypertensive emergencies possesses both positive and negative attributes. With several intravenous, short-acting, agents available, clinicians must make educated decisions about the best medication for their patients, and these decisions should be based on organ function as well as the patient's clinical presentation. The primary goal in hypertensive emergencies is to rapidly and safely reduce blood pressure to prevent further end-organ damage. Critical care nurses have an important role in the safe and effective management of these patients. The application of knowledge of treatment goals, hemodynamic monitoring, and pharmacological therapy for hypertensive emergencies can lead to the safe recovery of these critically ill patients. CCN

eLetters

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Financial Disclosures
None reported.

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CE Test

Test ID C1053: Recent Advances in the Treatment of Hypertensive Emergencies

Learning objectives: 1. Define hypertensive crisis 2. Describe the initial goal of treatment in hypertensive emergencies 3. Discuss the mechanism of action, onset of action, duration of action, adverse effects, dosage, and administration of clevidipine

1. Which of the following blood pressure measurements is indicative of a hypertensive crisis?
a. Diastolic pressure greater than 110 mm Hg
b. Diastolic pressure greater than 120 mm Hg
c. Systolic pressure greater than 160 mm Hg
d. Systolic pressure greater than 170 mm Hg

2. What is the target reduction in mean arterial pressure during a hypertensive emergency?
a. 10%
b. 15%
c. 20%
d. 25%

3. Which of the following adverse effects is associated with the administration of labetalol?
a. Reduced peripheral blood flow
b. Reduced cardiac output
c. Sinoatrial/atrioventricular node dysfunction
d. Increased peripheral vascular resistance

4. Which of the following medications may cause an acute allergic reaction in patients with a hypersensitivity to sulfite?
a. Labetalol
b. Sodium nitroprusside
c. Clevidipine
d. Fenoldopam

5. Sodium nitroprusside would be disadvantageous in patients with a stroke due to which of the following effects?
a. Increased intracranial pressure
b. Accumulation of cyanide
c. Increased intraocular pressure
d. Reduced regional blood flow

6. Clevidipine is classified as what type of drug?
a. Alpha receptor blocker
b. Beta receptor blocker
c. Calcium channel blocker
d. Sodium channel blocker

7. What is the onset of action for clevidipine?
a. 1 to 2 minutes
b. 2 to 4 minutes
c. 4 to 6 minutes
d. 6 to 8 minutes

8. How many kilocalories of lipids is contained in each milliliter of clevidipine?
a. 2
b. 4
c. 6
d. 8

9. Which percentage of patients in the VELOCITY study maintained blood pressure control on clevidipine monotherapy without the need for additional intravenous antihypertensive therapy?
a. 36%
b. 55%
c. 73%
d. 90%

10. What was the most common adverse reaction of clevidipine in the VELOCITY study?
a. Nausea and vomiting
b. Heart block
c. Pruritus
d. Bradycardia

11. What is the initial dosage of clevidipine for antihypertensive therapy?
a. 0.5 to 1 mg/h
b. 1 to 2 mg/h
c. 3 to 4 mg/h
d. 5 to 6 mg/h

12. Which of the following was the agent of choice for hypertensive emergencies for nonstroke patients in a survey of critical care physicians and pharmacists?
a. Clevidipine
b. Nicardipine
c. Labetalol
d. Sodium nitroprusside

Test answers: Mark only one box for your answer to each question. You may photocopy this form.

1. ❑a ❑b ❑c ❑d	2. ❑a ❑b ❑c ❑d	3. ❑a ❑b ❑c ❑d	4. ❑a ❑b ❑c ❑d	5. ❑a ❑b ❑c ❑d	6. ❑a ❑b ❑c ❑d	7. ❑a ❑b ❑c ❑d	8. ❑a ❑b ❑c ❑d	9. ❑a ❑b ❑c ❑d	10. ❑a ❑b ❑c ❑d	11. ❑a ❑b ❑c ❑d	12. ❑a ❑b ❑c ❑d

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