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Advances in Management of Acute Hypertension: A Concise Review

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Abstract

Chronic hypertension affects >1 billion people worldwide and >70 million people in the United States. Acute hypertensive episodes (AHE) are defined as severe spikes in blood pressure that may result in end-organ damage. Although AHE may arise independently as *de novo* events, they are more likely to occur in patients with pre-existing hypertension. One of the controversies regarding the clinical approach to AHE is the selection of antihypertensive medication. Depending on the clinical presentation of the patient and the threat of end-organ damage resulting from blood pressure elevation, appropriate and prompt treatment is warranted. There are multiple agents available for the management of hypertension. However, the greatest challenge lies in the acute care setting where the need exists for better initial and sustained control of blood pressure spikes. Many anti-hypertensive agents effectively lower blood pressure, yet only few have the capacity to achieve strict control of hypertension in the acute setting. Clevidipine butyrate is an ultra short-acting intravenous dihydropyridine calcium-channel blocker. Clevidipine has unique pharmacodynamic and pharmacokinetic properties that enable the fast, safe, and adequate reduction of blood pressure in hypertensive emergencies, with the ability to provide highly precise

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titration necessary to maintain a narrowly-defined target blood pressure range. Several recently published phase I, II, and III clinical studies have shown Clevidipine to be an effective blood pressure modulator in such capacity.

Introduction

Acute episodes of hypertension may arise in a variety of clinical settings due to the exacerbation of a pre-existing chronic hypertensive condition or as *de novo* phenomena (Varon, 2008; Vuylsteke *et al.*, 2000). Emergency, intensive care, anesthesia, and surgery are among the clinical settings where prompt recognition and treatment of acute hypertensive episodes (AHE) is of paramount importance. A variety of surgical and medical events may trigger intense sympathetic activity, resulting in sudden elevations in blood pressure (BP) (Awad and Goldberg, 2010).

If not recognized and treated immediately, AHE leave the patient at risk for end-organ damage and perioperative complications (Vaughan and Delanty, 2000). Consequently, it is important that practitioners be aware of current diagnostic and therapeutic approaches involved with management of hypertensive crises. Better utilization of existing therapies and the development of newer agents have improved the overall state of affairs, but the best treatment strategy for AHE is still a topic for debate. The aim of this article is to provide a concise review of therapeutic options for the management of AHE, with a focus on newer therapeutic options including intravenous clevidipine.

Hypertension: Differentiation and Classification and Epidemiology

Chronic hypertension affects approximately one billion people worldwide and an estimated 72 million people in the United States (Chobanian *et al.*, 2003). Despite significant efforts to increase awareness and promote preventive and early interventions, 30% of adults are still unaware of their hypertensive condition (Smithburger *et al.*, 2010). Several clinical classifications for chronic hypertension are currently utilized (Table 1).

Patients with chronic hypertension are more likely to experience AHE, including the possibility of associated end-organ damage. Overall, approximately 1% of hypertensive patients will experience an episode of AHE, known as hypertensive crisis (Kuppasani and Reddi, 2010; Owens, 2011). An AHE may also be the initial presentation in patients without a prior diagnosis of hypertension, signaling the new onset of hypertension as co-morbid condition. A hypertensive crisis is defined as an elevation in systolic blood pressure (SBP) >180 mmHg and diastolic blood pressure (DBP) >120 mmHg. It is imperative to distinguish between the two types of hypertensive crises — hypertensive emergency versus urgency. A *hypertensive emergency* is an elevation of BP >180/120 mmHg with evidence of end-organ damage to heart, kidneys, eyes, or brain (Chobanian *et al.*, 2003; Kuppasani and Reddi, 2010). *Hypertensive urgency* is defined as the same rise in BP, however with no concurrent evidence of end-organ damage (Chobanian *et al.*, 2003; Kuppasani and Reddi, 2010). The differences between these two entities are summarized in Table 2.

A number of recently published studies explored the clinical-epidemiological profile of patients presenting with hypertensive crises (Saguner *et al.*, 2010; Vilela-Martin *et al.*, 2011). One prospective study of risk factors showed that patients presenting with hypertensive crises were more likely to have morbidities including somatoform disorders, thyroid disease, and stroke (Saguner *et al.*, 2010). These patients also had greater prevalence of hypertensive heart disease and/or coronary artery disease (Saguner *et al.*, 2010). Non-compliance with anti-hypertensive regimens plays a significant role in hypertensive crises, and has been shown to be more prevalent in patients who experienced hypertensive crises

than those who had not (Saguner *et al.*, 2010). A greater incidence of non-compliance in women could potentially account for the increased prevalence of hypertensive crises observed in that group (Vilela-Martin *et al.*, 2011). However, men have a greater prevalence of hypertensive emergencies specifically, as well as complications attributable to AHE (Vilela-Martin *et al.*, 2011).

Vilela-Martin *et al.* (2011) found that patients with hypertensive emergencies were more likely to lead sedentary lifestyles and were older than those who presented with hypertensive urgencies. Furthermore, Caucasian patients were more likely to manifest hypertensive emergencies as opposed to hypertensive urgencies (Vilela-Martin *et al.*, 2011). In addition, more patients with hypertensive urgencies had a history of using antihypertensive medications (Saguner *et al.*, 2010; Vilela-Martin *et al.*, 2011). The epidemiology of hypertensive crises is similar to that of chronic hypertension, with African Americans and the elderly have higher rates of such crises (Varon, 2008).

Pathophysiology of Acute Hypertension

Although hypertension is among the most prevalent chronic medical conditions, the pathophysiology of hypertensive crises is still poorly understood (Kuppasani and Reddi, 2010; Smithburger *et al.*, 2010; Varon, 2008; Varon and Marik, 2003). Two processes thought to precipitate a hypertensive crisis are a sudden increase in systemic vascular resistance (SVR) and a failure of cerebral blood flow autoregulation, the mechanism that maintains blood flow at an appropriate level during changes in blood pressure (Smithburger *et al.*, 2010; Varon, 2008). While a hypertensive crisis can present without a documented history of hypertension, the acute nature of these events suggests an underlying hypertensive condition coupled with the presence of an additional inciting factor or event (Varon, 2008). For example, in the perioperative setting, stimuli such as elevated BP during anesthesia induction, tracheal intubation, and emergence from anesthesia can be the initiating event for the hypertensive crisis (Awad and Goldberg, 2010). Anesthesia induction alone can cause an increase of 20 mmHg in normotensive patients, and up to 90 mmHg in patients with a pre-existing hypertensive condition (Ahuja and Charap, 2010).

Vascular endothelial injury may result from repeated instances of acute hypertension, associated with elevated systemic vascular resistance. As blood pressure increases, vessel walls are subjected to stress, which leads to the release of vasoconstrictors resulting in further endothelial damage (Kuppasani and Reddi, 2010; Smithburger *et al.*, 2010; Vaughan and Delanty, 2000). If not promptly treated, a cycle of clotting cascade activation, arteriole tissue death and accumulation, neurohormonal system upregulation, induction of oxidative stress, and inflammatory cytokines develops (Kuppasani and Reddi, 2010). Deposition of platelets and fibrin, vasoconstriction, and thrombosis, as a result of vascular injury, result in decreased blood flow and supply to and from organs (hypoperfusion and ischemia) (Kuppasani and Reddi, 2010; Smithburger *et al.*, 2010). If this vicious cycle is not terminated, autoregulatory dysfunction becomes imminent (Polly *et al.*, 2011).

Autoregulation is crucial to maintenance of adequate perfusion of the kidney, heart, and brain. These organs require specific amounts of oxygen to function, and reduced blood flow can lead to ischemia and organ injury. Autoregulation occurs in many body tissues, but has best been studied in cerebral blood flow. When blood pressure is severely elevated there is a right shift in the autoregulation curve, resulting in cerebral blood flow at higher mean arterial pressures (Belsha, 2011; Kessler and Joudeh, 2010; Vaughan and Delanty, 2000). In order to avoid hyperperfusion of tissues, blood pressure in these patients must be lowered carefully so that hypoperfusion does not occur (Belsha, 2011; Kessler and Joudeh, 2010). Therefore caution must be used when selecting an antihypertensive agent to manage AHE.

In the blood pressure range between 60 mmHg and 140 mmHg, cerebral blood flow is "autoregulated" extremely well. In hypertensive patients, autoregulation occurs with mean arterial pressure (MAP) up to 180 mmHg (shifted to the right), though the blood flow remains constant. During hypertensive crises, the shift in the autoregulatory curve often fails to occur, putting patients at risk for cerebral hyperperfusion (Belsha, 2011). When the corresponding increase in BP crosses the autoregulatory range, compensatory mechanisms cease (Belsha, 2011). Vasodilation and endothelial dysfunction occurs, which may lead to cerebral fluid buildup (edema), ultimately followed by cerebral spasm (eclampsia) and ischemia (Kuppasani and Reddi, 2010). Continuation of this "vicious" cycle results in the severe, acute elevation in BP.

Initial Recognition of Acute Hypertension

Quick determination of a treatment plan for patients experiencing hypertensive crisis is essential. Healthcare providers should focus on obtaining a complete history including any previous diagnosis of hypertension/cardiovascular disorders/endocrine disorders (diabetes for instance), medications, surgeries, and symptoms. Medication history is important to assess compliance (Kessler and Joudeh, 2010). Hypertensive emergency patients present with symptoms such as nausea, headache, vomiting, chest pain, dyspnea, vertigo, and neurologic symptoms (Katz *et al.*, 2009). These symptoms are similar to those of hypertensive urgency, so it is necessary to triage patients in order to decide the correct method of treatment.

Hypertensive emergency patients present with symptoms of end-organ damage; these symptoms are absent in hypertensive urgencies (Vaughan and Delanty, 2000). Blood pressure should be measured on both arms in order to determine if there is a significant difference between the two. A significant difference in the BP could indicate the presence of aortic bleeding, or dissection.

Current guidelines suggest that the physical exam should include a fundoscopic, cardiovascular, pulmonary, and neurologic exam. Any evidence of hemorrhaging, excess circulatory fluid, or optic swelling (papilledema) found on the fundoscopic exam indicates a hypertensive emergency (Vaughan and Delanty, 2000). Volume status should be estimated as accurately as possible, because end-organ damage can result from volume overload or depletion. No standardized guidelines for laboratory testing exist; however, a urine analysis, electrolytes, creatinine, and complete blood count should be performed immediately. Additionally, an electrocardiogram and chest x-ray may be necessary to determine the presence of organ damage (Kessler and Joudeh, 2010; Kuppasani and Reddi, 2010; Vaughan and Delanty, 2000). A study of the STAT registry found that brain imaging is performed more frequently than other conventional approaches such as urine analysis and fundoscopy (Katz *et al.*, 2009).

The organs most susceptible to end-organ damage associated with hypertensive emergencies include the eye, kidney, heart, and brain (Belsha, 2011; Polly *et al.*, 2011). Thus, a physician's clinical evaluation should focus on these organ systems. Common conditions associated with hypertensive emergencies include: acute aortic dissection, acute left ventricular failure with pulmonary edema, acute myocardial infarction (MI), acute renal failure, eclampsia, and ischemic and hemorrhagic stroke (Kuppasani and Reddi, 2010). Cerebral edema and neurological dysfunction may result from acute hypertension, a condition known as hypertensive encephalopathy (Strandgaard and Paulson, 1989). Some symptoms of these disorders include chest pain (MI, aortic dissection), back pain (aortic dissection), neurological symptoms, seizures, or altered consciousness (hypertensive encephalopathy), papilledema, hemorrhages, and exudates (eye damage) (Vaughan and

Delanty, 2000). To prevent end-organ damage, prompt treatment with intravenous anti-hypertensives is often required.

Initial Treatment of Hypertension

Guidelines by the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure for treating hypertensive emergencies include immediate intervention with a goal of reducing SBP by 10 to 15%, but no more than 25% within the first hour. Reduction of the absolute BP to 160/110 mmHg should be done gradually over the following two to six hours (Aggarwal and Khan, 2006; Chobanian *et al.*, 2003; De Gaudio *et al.*, 2009; Flanigan and Vitberg, 2006; Hays and Wilkerson, 2010; Pollack and Varon, 2008; Polly *et al.*, 2011; Smithburger *et al.*, 2010; Varon, 2008). In cases of aortic dissection, the SBP should be reduced to less than 120 mmHg within twenty minutes. In hypertensive emergencies associated with ischemic stroke, BP must be decreased to less than 185/110 before thrombolytic therapy may be administered (De Gaudio *et al.*, 2009; Hays and Wilkerson, 2010; Pollack and Varon, 2008; Polly *et al.*, 2011; Varon, 2008). If BP reduction occurs too quickly, there may be a significant decrease in blood flow to tissues with cell death as a possible outcome (De Gaudio *et al.*, 2009; Polly *et al.*, 2011; Smithburger *et al.*, 2010; Varon, 2008). Since overshooting a target BP (hypoperfusion) is associated with poor results, many treatment protocols require strict arterial BP monitoring (Pollack and Varon, 2008; Rhoney and Peacock, 2009).

Hypertensive emergency should be treated aggressively, using quick-onset intravenous medications, whereas hypertensive urgency does not always require such aggressive treatment. Longer acting oral medications such as labetolol and clonidine may be more appropriate in situations of hypertensive urgency. However, caution should be exercised when using anti-hypertensive agents in the acute setting. An overly aggressive treatment approach may lead to organ hypoperfusion (as mentioned above) (Rodriguez *et al.*, 2010). Therefore, achieving the aforementioned reduction goal timeline decreases the likelihood of organ hypoperfusion and further organ injury. Once the immediate threat of organ damage is diminished, BP should be gradually controlled to the baseline within a period of 24–48 hours (Peacock *et al.*, 2009). Longer acting treatments, such as beta blockers, may be more appropriate during such gradual stabilization situations.

The ideal intervention for management of hypertensive emergency is easily prepared and administered, has a rapid onset of action, is rapidly titratable, has a short duration of action, is well tolerated, has a low incidence of toxicity or adverse side effects, has few contraindications, allows for dosage adjustment, has vascular selectivity, is inexpensive, and had predictable effects (Aronson *et al.*, 2008; Awad and Goldberg, 2010; Deeks *et al.*, 2009; Ndefo *et al.*, 2010; Owens, 2011; Peacock *et al.*, 2009; Pollack and Varon, 2008; Polly *et al.*, 2011; Smithburger *et al.*, 2010). Intravenous administration is also preferred to oral treatment as it allows for a faster onset of action and is typically associated with ease of titration in this setting. The most commonly used agents, with their advantages and disadvantages are outlined in Table 3.

Many intravenous and oral anti-hypertensive agents are available, but most treatments do not encompass optimal benefit versus risk profiles for a broad range of hypertensive emergency situations. Therefore the patient's medical conditions as well as the preference of individual prescribers and institutions need to be taken into account when choosing among different agents (Belsha, 2011; Pollack and Varon, 2008). Calcium-channel blockers, which inhibit L-type calcium channels, and specifically the subclass of dihydropyridines (nifedipine, nicardipine, clevidipine, etc.), are commonly considered a first-line treatment of hypertensive emergencies because they are strong vasodilators and have few negative effects

on cardiac conduction and contractility when compared to classes such as beta blockers (Eisenberg *et al.*, 2004).

Clevidipine for the Treatment of Acute Hypertension

The realm of intravenous anti-hypertensive therapy has remained stagnant for the past decade until the introduction of clevidipine. Clevidipine is a third-generation, intravenous, dihydropyridine calcium-channel antagonist. It was approved by the United States Federal Food and Drug Administration in 2008 for the reduction of blood pressure when oral therapy is not feasible or desirable.

The novelty of clevidipine is the ultra short half-life of about 1 minute and its potent arterial vasodilation ability without affecting venous capacitance or myocardial contractility (Rivera *et al.*, 2010; Smithburger *et al.*, 2010; Varon and Marik, 2008). Clevidipine reduces the pressure that the heart's ventricles must generate to eject blood, yet has little to no effect on the pressure of blood that fills the heart's chambers prior to contraction (Varon, 2008). This results in the same volume of blood being pumped out of the heart, with less resistance to blood ejection, thereby protecting against inadequate blood flow to the heart's muscle and preserving coronary endothelial function. These effects are due to the minimal effects of the agent on stroke volume, cardiac output, or heart rate (Peacock *et al.*, 2009). Clevidipine also appears to have no significant adverse effect on heart rate (Aronson *et al.*, 2008; Polly *et al.*, 2011).

Clevidipine is available as an injectable emulsion and can be administered via a peripheral or a central venous catheter. This product is contraindicated in patients with allergies to soy products, eggs and egg products, or defective lipid metabolism. Clevidipine is rapidly metabolized by blood and tissue esterases into inactive metabolites (Rivera *et al.*, 2010). Approximately 99.5% of clevidipine in plasma is protein bound. It is also cleared at a high rate primarily through urine (63–74%) and feces (7–22%) (Smithburger *et al.*, 2010). Clevidipine's pattern of metabolism makes it safe for patients with hepatic and renal dysfunction (Rivera *et al.*, 2010).

Clevidipine's characteristics, which include rapid onset of effect, high clearance, and small volume of distribution, make it an ideal agent for the management of acute severe hypertension. Several recent studies have evaluated clevidipine's efficacy in the perioperative setting. Two large randomized, double-blind, placebo controlled trials (ESCAPE1 and ESCAPE 2) have evaluated clevidipine in the pre- and postoperative periods, respectively (Rivera *et al.*, 2010). ESCAPE 1 was the first trial to demonstrate the efficacy of clevidipine, showing a decrease in systolic pressure by at least 15% from baseline, achieving this within a mean of 6 minutes post-infusion (Levy *et al.*, 2007).

The ECLIPSE trial was the first large randomized controlled trial evaluating the efficacy of clevidipine compared to other anti-hypertensive agents (sodium nitroprusside, nitroglycerin, and nicardipine) for the management of perioperative hypertension (Singla *et al.*, 2008). ECLIPSE consisted of three parallel arms in which adult cardiac surgery patients were randomized to either clevidipine or one of the comparator agents. When comparing clevidipine (n=751) to the pooled comparator groups (n=756), clevidipine demonstrated superior BP control within the predefined ranges of 75 to 145 mmHg pre- and postoperatively and 95 to 135 mmHg intraoperatively. This finding was sustained when the ranges were tightened to 105 to 145 mmHg pre- and postoperatively and 95 to 135 mmHg intraoperatively in a post-hoc analysis. Compared with clevidipine, nitroprusside was shown to have significantly more excursions both above and below the target range while nitroglycerin resulted in significantly more excursions above the range. Nitroprusside was

also associated with a significantly higher 30-day mortality rate compared to clevidipine (4.7 vs. 1.7%, p=0.004).

Unlike the other comparator agents, nicardipine had similar efficacy in maintaining BP within the predetermined range of 75 to 145 mmHg pre- and postoperatively and 95 to 135 mmHg intraoperatively, although clevidipine had fewer excursions when the range was tightened to 105 to 145 mmHg pre- and postoperatively and 95 to 135 mmHg intraoperatively in a post-hoc analysis (Aronson *et al.*, 2008). The data emerging from the ECLIPSE trial also suggest that perioperative BP needs to be more tightly controlled than previously thought, since even a 1 mmHg excursion outside of range, when sustained for 60 minutes or longer, can be prognostically important (Aronson *et al.*, 2008). The data also demonstrate the importance of being able to avoid hypoperfusion when treating acute elevations of BP.

The safety and efficacy of clevidipine specifically for the management of hypertensive crises was evaluated in the VELOCITY study, a phase III, open-label, single-arm, multicenter study (Pollack *et al.*, 2009). This study demonstrated the ability of clevidipine to quickly achieve BP within a target range with minimal episodes of excursion below the target range. Within 30 minutes after initiation of the clevidipine infusion, 104 of 117 (88.9%) patients in the efficacy population achieved SBP within their target range. Only 2 patients of 126 (1.6%) in the safety population experienced a decrease in SBP below the lower limit of their initial target range. Findings from VELOCITY were consistent with the other large trials, further demonstrating clevidipine to be a safe and efficacious drug for treating acute hypertension (Pollack *et al.*, 2009).

The ACCELERATE trial was a recently completed multicenter, single arm study evaluating clevidipine for the management of severe hypertension with intracerebral hemorrhage (ICH) (Graffagnino *et al.*, 2009). Clevidipine, as an anti-hypertensive monotherapy, was shown to be effective at rapid BP lowering with 97% of patients (29 of 30) achieving the target SBP of less than 160 mmHg within 30 minutes. The majority of patients achieved the target goal shorter than 30 minutes with a median time to target SBP of 6.5 minutes (95% CI 3–10). However, three hypotensive episodes were reported in association with clevidipine infusion, with BP increasing promptly after the clevidipine infusion rate was decreased or discontinued.

Readmission After Treatment

Little is known about the rate of readmission following acute hypertension. A retrospective study using the STAT registry was conducted in order to determine the rate of readmission and the characteristics of readmitted patients (Gore *et al.*, 2010). The highest rate of readmission occurred during the first three weeks following discharge. One third of acute hypertension patients discharged from the hospital were readmitted within 90 days. Approximately 29% of those patients were readmitted for hypertension while 71% were readmitted for other reasons (Gore *et al.*, 2010). Several factors were associated with the readmissions for hypertension, including non-compliance with the hypertensive treatment regimen, substance abuse, dialysis use for chronic kidney disease, prior hospitalizations for acute hypertension, and presentation to the hospital with shortness of breath or seizures. In addition, these patients were younger than those who were not readmitted or were readmitted for other diagnoses. Lastly, patients with private insurance had fewer re-hospitalizations than those with insurance from the government (Gore *et al.*, 2010). Due to the significant percentage of patients who were re-hospitalized, further research needs to be done in order to determine the effect of patient history and socioeconomic variables on the rate of re-hospitalization (Gore *et al.*, 2010).

Conclusion

With regards to the management of hypertensive crises, the debate is still ongoing about the best treatment strategies. First, the medical history of the patient should be taken into consideration when deciding the most effective treatment course. A goal for target blood pressure should be set, including the timing for the gradual lowering of blood pressure. The goal blood pressure should be based on the co-morbidities of the patient as well as the clinical presentation of the patient. This knowledge should factor into the decision as to whether the patient receives longer or shorter acting and oral or intravenous anti-hypertensives.

Overly aggressive attempts to lower blood pressure may cause unintentional hypotension and associated organ hypoperfusion, especially in patients whose homeostatic mechanisms are dependent on the higher “baseline” blood pressure for adequate tissue oxygen delivery. On the other hand, inadequate lowering of BP may occur, leaving the patient at risk for continued severe hypertension, and a further increase in morbidity and mortality. A “roller coaster” effect of oscillating between overshooting BP (causing hypotension) and using treatments (i.e., vasopressors) to “correct” the blood pressure to normotensive levels may be damaging to end organs and the vasculature. Without precise control of BP in hypertensive crisis situations, the “roller coaster” effect — oscillating between hypertension and hypotension — is a challenge to treating physicians.

Due to its rapid onset and offset properties, ultra-short half-life, and ease of titration, clevidipine may offer an attractive alternative for patients who stand to benefit from more precise titration and control during anti-hypertensive therapy. However, there is limited data on guidance when tight control of BP is truly indicated. Clinical trial data regarding clevidipine indicate the drug is effective in the treatment of hypertensive crises in patients requiring an initial rapid lowering of blood pressure, without increased risk of over shooting the target BP range, allowed by precise 24–48-hour BP control at the desired level.

Current guidelines for treatment of acute hypertension may be too broad. Future studies should focus on the management of acute hypertension in specific patient populations, with evaluation of the relationship between various anti-hypertensive therapies in the context of patient population and additional focus on safe, rapid, and effective titration. We recommend the following areas of exploration:

- Management of acute hypertension in specific populations (race, sex, obesity, ambulatory patients, critically ill patients).
- Management of interventions in specific co-morbid conditions.
- Advanced techniques (intravenous, transdermal, oral, rectal) for rapid, effective titration and delivery of medications.
- Methods of delivery and pharmacological options in particular patient volume states (renal failure, car diac disease, dehydration/depletion).
- Better articulation of the definition of end-organ damage in a specific organ system and the limits to which that system may be injured and still achieve functional recovery.
- Use of adjunct medications and techniques to augment the efficacy of the current anti-hypertensive armamentarium.

Ultimately, achieving acute blood pressure control should take into account patient co-morbidities, medications and their usage adherence, clinical presentation, and procedures, if applicable.

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Table 1

Classification of Blood Pressure for Adults Aged ≥18.

Category	Systolic Blood Pressure	Diastolic Blood Pressure
Normal	<120	<80
Pre-hypertension	120–139	80–89
Hypertension-Stage I	140–159	90–99
Hypertension-Stage II	≥160	≥100
Hypertensive Urgency	>180	>120
Hypertensive Emergency	>180	>120 and target organ damage

Adapted from Chobanian, 2003.

Table 2

Characteristics of Hypertensive Emergency Versus Hypertensive Urgency.

	Hypertensive Emergency	**Hypertensive Urgency**
Significant elevation in BP	Yes	Yes
BP>180/120	Yes	No
Target organ damage	Yes	No
IV Medications Required	Yes	No
Associated Conditions	Heart attack, aortic bleeding, optic swelling, hypertensive encephalopathy, excess circulatory fluid	Nose bleeds, severe hypertension, scleroderma

Adapted from Kuppasani *et al*, 2010.

Table 3

Properties and Indications of Anti-hypertensive Medications. Part 1.							
Drug	**Class/Mechanism/Properties**	**Common Uses**	**Cautions & Contraindications**	**Dosing**	**Onset**	**Duration**	**Side Effects**
Esmolol	Beta-adrenergic antagonist, cardioselectively blocks beta-1 receptors, negative chronotropic and inotropic agent, lacks vasodilator properties, high plasma clearance, decreases heart rate, cardiac output, and stroke volume	Aortic dissection (with sodium nitroprusside, nicardipine, or clevidipine), acute pulmonary edema, hypertensive encephalopathy (with vasodilators to reduce reflex tachycardia)	Caution with renal impairment or restricted lung disease, contraindications include severe bradycardia, bronchial asthma, cardiac conduction disorders including cardiogenic shock and heart failure, heart block greater than first degree, pregnancy, and uncompensated cardiac failure	Load 250–1000 μg/kg over 1–3 min, can infuse 25–100 μg/kg/min, titrate every 5–20 min with a repeat bolus and increase drip by 25–50 μg/kg/min up to a max dose of 300 μg/kg/min	1–5 min with a max effect after 5 min	10–30 min after infusion is stopped	Acute pulmonary edema, bradycardia, bronchospasm, diaphoresis, dizziness, first degree heart block, flushing, hypotension, nausea, seizures, somnolence, thrombophlebitis, abrupt withdrawal may cause chest pain
Fenoldopam	Dopamine-1 receptor blocker, selectively vasodilates peripheral arteries, primary action in proximal and distal renal tubules, reduces peripheral vascular resistance, blocks sodium reabsorption resulting in diuresis and natriuresis, decreases systemic blood pressure BP, increases renal blood flow, improves creatinine clearance, sodium clearance, and urine flow	Acute ischemic stroke, acute pulmonary edema or hypertensive encephalopathy if patient has acute or chronic renal failure, microangiopathic anemia, and sympathetic crisis	Contraindicated in glaucoma patients as it causes a dose-dependent rise in intraocular pressure	0.1 μg/kg/min with titrated infusion in 0.05–0.1 μg/kg/min increments up to a max of 1.6 μg/kg/min	5–10 min with a max effect after 15–30 min	Up to 1 hr after infusion is stopped	Atrial fibrillation, dizziness, flushing, headaches, hypokalemia, hypotension, nausea, reflex tachycardia, worsening angina
Labetalol	Mixed alpha-1 and beta-1 & −2 adrenergic recaptor blocker (alpha:beta activity ratio of 1:3 orally and 1:7 with IV use), negative chronotropic and inotropicagent, possesses vasodilator properties, controls reflex tachycardia as BP falls, reduces afterload, no effect on cardiac and cerebral blood flow, cardiac output, or renal function	Acute ischemic stroke or intracerebral hemorrhage (ICH), acute myocardial infarction (MI), acute pulmonary edema, aortic dissection (with use of a vasodilator such as sodium nitroprusside, nicardipine, or clevidipine), eclampsia, hyperadrenergic conditions such as cocaine intoxication, hypertensive emergency with acute or chronic renal failure, and hypertensive encephalopathy, safely used in pregnancy	Caution in diabetes or hepatic impairment, contraindications include bronchial asthma, cardiogenic shock, chronic obstructive pulmonary disease, heart block greater than first degree, pheochromocytoma, reactive airway disease, severe bradycardia, and uncompensated cardiac failure	20 mg IV over 2 min with additional repeated IV boluses every 10 min with escalating doses of 40 mg, 80 mg to a max, cumulative dose of 300 mg, a short-term IV infusion of 0.5–2.0 mg/min may also be used	2–5 min with a max effect after 5–15 min	2–6 hrs after infuseion is stopped	Bradycardia, bronchospasm, dizziness, nausea, paresthesia, profound hypotension, profound orthostasis, scalp tingling, sinoatrial/atrioventricular nodal dysfunction such as heart block, vomiting, abrupt withdrawal may cause acute tachycardia, ischemia, and rebound hypertension

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Properties and Indications of Anti-hypertensive Medications. Part 1.

Drug	Class/Mechanism/Properties	Common Uses	Cautions & Contraindications	Dosing	Onset	Duration	Side Effects
Nicardipine	Second-generation dihydropyridine-derived calcium channel antagonist, selectively blocks L-type voltage-sensitive calcium channels of the heart, cerebral arterial vasodilator, allows peripheral arteriolar smooth muscle to be relaxed, causes decreased peripheral vascular resistance	Acute ischemic stroke or ICH, acute MI, acute pulmonary edema, aortic dissecttion (with use of esmolol or labetalol), eclampsia, hypertensive encephalopathy, sympathetic crisis, may be used safely in pregnancy	Caution in hepatic and renal impairments, contraindicated in advanced or pre-existing aortic stenosis	Independent of body weight, 5–10 mg/hr bolus which can be increased by 2.5 mg/hr every 5–15 min to a max of 15 mg/hr	5–15 min	2–6 hrs after infusion is stopped	Digital gysesthesia, dizziness, edema, flushing, headaches, hypotension, nausea, tachycardia, vomiting, abrupt withdrawal may cause hypertension or rebound angina
Sodium Nitroprusside	Non-selectively directly dilates arteries and veins through the generation of cyclic guanosine monophosphate (cGMP), reduces both the preload as well as the afterload	Acute pulmonary edema, aortic dissecttion (with use of esmolol or labetalol), heart failure and adrenergic crisis, and hypertensive crises complicated by hypertensive encephalopathy if necessary	Caution in increased intracranial pressure or renal impairment, contraindicated in acute coronary syndrome (ACS), acute MI, ischemic or hemorrhagic stroke, and severe coronary artery disease (CAD)	0.25–1.0 μg/kg/min that may increase by 0.5 μg/kg/min as needed with an average effective dose of 3 μg/kg/min, (difficult to administer as it requires an intraarterial line to monitor blood pressure and inactivated by light so the IV bag and infusion tubing must be protected)	1–2 min	1–4 min after the infusion is stopped	Cerebral edema, coronary steal in patients suffering from CAD (because of the afterload reduction of regional blood flow), diaphoresis, drug tolerance, flushing, headaches, hypotension, increased intracranial pressure, muscle twitching, nausea, precipitous falls in blood pressure leading to overshoot and tissue perfusion, reflex tachycardia, vomiting, abrupt withdrawal may cause rebound hypertension. May also be a toxic accumulation of cyanide (CN), especially in patients with hepatic and renal impairments or who have had prolonged infusions lasting longer than 2 days (CN toxicity is often asymptomatic but sometimes may cause acidosis, cardiac arrest, coma, encephalopathy, focal neurologic damage, hypoxia, and seizures).

Properties and Indications of Anti-hypertensive Medications. Part 2.							
Drug	**Class/Mechanism/Properties**	**Common Uses**	**Cautions & Contraindications**	**Dosing**	**Onset**	**Duration**	**Side Effects**
Nitroglycerin	Direct venous vasodilator, ineffective arterial dilator, reduces both cardiac output and preload, not particularly useful for hypertensive emergencies	Acute coronary syndrome, acute MI, ischemic heart disease, pulmonary edema, and after coronary bypass surgery	Contraindications include constrictive pericarditis, pericardial tamponade, restrictive cardiomyopathy, and the concurrent use of phosphodiesterase inhibitors like sildenafil and vardenafil	5 μcg/kg/min that initially may rise by 5 μcg/min every 3–5 min until the dose is 20 μcg/min and then may increase by 10 μcg/min every 3–5 min to a max of 100–200 μcg/kg/min	1–5 min	5–20 min	(Volume dependent) dizziness, drug tolerance, headaches, hypotension, hypoxemia, reflex tachycardia, worsening ischemia
Enalaprilat	Arterial vasodilator, intravenous form of the angiotensin-converting-enzyme (ACE) inhibitor enalapril	Congestive heart failure	Caution in hypertrophic cardiomyopathy, ischemic heart disease, preexisting renal insufficiency, severe aortic stenosis, and unstented renal artery stenosis	1.25 mg IVP over 5 min at 4–6 hr intervals with a max of 6 mg in 6 hours	15–30 min with a max effect after 4 hrs	12–24 hrs	(BP response is variable, unpredictable, and not dose-dependent) cough, dizziness, headaches, hypotension in high renin states, hyperkalemia, oliguria
Hydralazine	Direct arterial vasodilator, decreases afterload, not teratogenic, increases uterine blood flow	Hypertensive emergencies of pregnancy and eclampsia	Not suggested for any other hypertensive emergencies	5–10 mg bolus followed by 5–10 mg IV every 20–30 min as needed	10–30 min	1–6 hrs	Fluid retention, flushing, headaches, nausea, significant reflex tachycardia, and the precipitation of MIs
Phentolamine	Alpha-1 & −2 adrenergic receptor blocker, increases sympathetic activity, positive chronotropic and inotropic effects on heart	Catecholamine toxicity and sympathetic crises such as amphetamine overdose, cocaine toxicity, clonidine withdrawal, and pheochromocytoma	Contraindications include coronary and cerebral arteriosclerosis and renal impairment	1–5 mg bolus while repeat bolus dosing can be administered as needed every 5–15 min reaching a max of 15 mg	1–2 min	10–30 min	Flushing, dizziness, headache, miosis, nasal congestion, nausea, reflex tachycardia, vomiting, angina or MI in CAD patients

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