Review

Clinical review: The management of hypertensive crises

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Abstract

Hypertension is an extremely common clinical problem, affecting approximately 50 million people in the USA and approximately 1 billion individuals worldwide. Approximately 1% of these patients will develop acute elevations in blood pressure at some point in their lifetime. A number of terms have been applied to severe hypertension, including hypertensive crises, emergencies, and urgencies. By definition, acute elevations in blood pressure that are associated with end-organ damage are called hypertensive crises. Immediate reduction in blood pressure is required only in patients with acute end-organ damage. This article reviews current concepts, and common misconceptions and pitfalls in the diagnosis and management of patients with acutely elevated blood pressure.

Keywords aortic dissection, β-blockers, calcium channel blockers, fenoldopam, hypertension, hypertensive crises, hypertensive encephalopathy, labetalol, nicardipine, nitroprusside, pregnancy

Hypertension is an exceedingly common disorder in western societies, and as such practitioners of most clinical specialties are likely to encounter patients with acute, severe elevations in blood pressure. In particular, hypertensive emergencies and hypertensive urgencies (see the section on Teminology, definitions, and misconceptions, below) are commonly encountered in the emergency department, operating room, postanaesthesia care unit, and intensive care units [1–8]. The most important factor that limits morbidity and mortality from these disorders is prompt and carefully considered therapy [9]. Unfortunately, hypertensive emergencies and urgencies are among the most misunderstood and mismanaged of acute medical problems seen today. Indeed, the reflex of rapidly lowering an elevated blood pressure is associated with significant morbidity and death. Clinicians dealing with hypertensive emergencies and urgencies should be familiar with the pathophysiology of the disease and the principles of treatment. This article reviews current concepts, and common misconceptions and pitfalls in the diagnosis and management of patients with severe hypertension.

Terminology, definitions, and misconceptions

Efforts to classify hypertension on the basis of specific values have existed for the past 100 years. In the USA, the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure has classified hypertension according to the degree of elevation in blood pressure [1,10]. According to the most recent report by this committee (the JNC 7 Report [10]), patients with stage 1 hypertension have a systolic blood pressure of 140–159 mmHg or a diastolic blood pressure of 90–99 mmHg. Those patients with stage 2 hypertension have a systolic blood pressure greater than 160 mmHg or a diastolic blood pressure greater than 100 mmHg. Although not specifically addressed in the JNC 7 Report, patients with a systolic blood pressure greater than 179 mmHg or a diastolic blood pressure that is greater than 109 mmHg are usually defined as having 'severe or accelerated' hypertension.

A number of different terms have been applied to acute severe elevations in blood pressure, and the current terminology is somewhat confusing. However, most authorities have defined hypertensive crises or emergencies as a sudden increase in systolic and diastolic blood pressures associated with 'acute end-organ damage' (i.e. cardiovascular, renal, central nervous system) that requires immediate management. On the other hand, the term 'hypertensive urgency' has been used for patients with severely elevated blood pressure without acute

end-organ damage [2–5,8,11,12]. It is important to emphasize that the clinical distinction between hypertensive emergencies (crises) and hypertensive urgencies depends on the presence of acute target organ damage, rather than the absolute level of blood pressure. Table 1 lists those clinical conditions that meet the diagnostic criteria for hypertensive emergencies. The term 'malignant hypertension' has been used to describe a syndrome characterized by elevated blood pressure accompanied by encephalopathy or acute nephropathy [1,13]. However, this term has been removed from national and international blood pressure control guidelines [1,10], and this condition is best referred to as a hypertensive emergency or crisis.

The dynamic physiologic changes that occur in the early postoperative period deserve special mention. Postoperative hypertension has arbitrarily been defined as a systolic blood pressure greater than 190 mmHg and/or diastolic blood pressure greater than 100 mmHg on two consecutive readings following surgery [14,15]. Postoperative hypertension may have significant adverse sequelae in both cardiac and noncardiac patients [16]. The transient but potentially life-threatening nature of postoperative hypertension and the unique clinical factors present in the postoperative period require that this clinical syndrome be given individual consideration. Another group of patients that requires special mention is those pregnant patients who develop elevations in blood pressure during, immediately before, or after delivery. The presence of a systolic pressure greater than 169 mmHg or a diastolic pressure greater than 109 mmHg in a pregnant woman is considered a hypertensive emergency that requires immediate pharmacologic management [3,17,18].

Table 1

Hypertensive emergencies/crises
Hypertensive encephalopathy
Dissecting aortic aneurysm
Acute left ventricular failure with pulmonary edema
Acute myocardial ischemia
Eclampsia
Acute renal failure
Symptomatic microangiopathic hemolytic anemia

Epidemiology

Hypertension is an extremely common clinical problem in western countries. Hypertension affects approximately 50 million people in the USA and approximately 1 billion individuals worldwide [1,19,20]. Most of these patients have essential hypertension and approximately 30% are undiagnosed [1,19,21]. Furthermore, only between 14% and 29% of American patients with hypertension have adequate blood pressure control [19]. The incidence of hypertension increases with age. In the Framingham heart study [20] the incidence of hypertension increased in men from 3.3% at age 30–39 years to 6.2% at age 70–79 years. Overall, the prevalence and incidence of hypertension are slightly higher in men than in women [19,20,22,23]. The incidence of hypertension in African-Americans is about twofold higher than in whites [19,20,22,23]. The prevalence and incidence of hypertension in Mexican-Americans are similar to or lower than those in non-Hispanic whites [19,23,24].

The syndrome of hypertensive emergency was first described by Volhard and Fahr in 1914 and was characterized by severe accelerated hypertension, accompanied by evidence of renal disease and by signs of vascular injury to the heart, brain, retina and kidney, and by a rapidly fatal course ending in heart attack, renal failure, or stroke [25]. The first large study of the natural history of malignant hypertension was published in 1939 before the widespread use of antihypertensive agents [26]. In that seminal report by Keith and colleagues, untreated malignant hypertension had a 1-year mortality of 79% and a median survival of 10.5 months.

It has been estimated that approximately 1% of patients with hypertension will develop a hypertensive crises at some point during their lives [27,28]. Before the advent of antihypertensive therapy, this complication occurred in up to 7% of the hypertensive population [29]. The epidemiology of hypertensive crises parallels the distribution of essential hypertension in the community, being much higher among African-Americans and the elderly; however, men are affected two times more frequently than are women [9,12,30,31]. Most patients who present with a hypertensive crisis have previously been diagnosed as hypertensive and many have been prescribed antihypertensive therapy with inadequate blood pressure control [9,12,30]. The lack of a primary care physician and failure to adhere to prescribed antihypertensive regimens are major risk factors for hypertensive emergencies [32]. Tumlin and colleagues [33] reported that only 51 out of 94 (54%) patients presenting to an emergency room with a hypertensive emergency had taken their hypertensive medication in the preceding week. Illicit drug use has also been reported to be a major risk factor for the development of hypertensive emergency [32].

Despite the development of increasingly effective antihypertensive treatments over the past 4 decades, the incidence of hypertensive crisis has increased. Hospital admissions for hypertensive emergency more than tripled between 1983 and 1990, from 23 000/year to 73 000/year in the USA [34]. The reported incidence of postoperative hypertensive crisis varies depending on the population examined, with most studies reporting an incidence of between 4% and 35% [15,35,36]. Like other forms of accelerated hypertension, patients with postoperative hypertensive crisis usually have a prior history of poorly controlled hypertension [21]. Pregnancy-related

hypertension (pre-eclampsia) is a form of hypertension that deserves special mention. Pre-eclampsia occurs in about 7% of all pregnancies but the incidence varies according to the patient population, with 70% being nulliparous and 30% parous [37].

Etiology and pathophysiology

Malignant hypertension can develop *de novo* or can complicate underlying essential or secondary hypertension (Table 2). In white patients, essential hypertension accounts for 20–30% of malignant hypertension. In blacks, however, essential hypertension is the predominant cause of malignant hypertension, accounting for approximately 80% of all cases [38,39]. Renal parenchymal disease accounts for up to 80% of all secondary causes, with chronic pyelonephritis and glomerulonephritis being the most common diagnoses [38]. The average age of presentation of essential malignant hypertension tends to be higher than that for secondary causes. Secondary causes are almost always found in white patients presenting under the age of 30 years, whereas black patients can present with essential hypertension at a younger age.

Table 2

Secondary causes of malignant hypertension

Cause	Example
Renal parenchymal	Chronic pyelonephritis Primary glomerulonephritis Tubulointerstitial nephritis
Systemic disorders with renal involvement	Systemic lupus erythematosus Systemic sclerosis Vasculitides
Renovascular	Atherosclerotic disease Fibromuscular dysplasia Polyarteritis nodosa
Endocrine	Pheochromocytoma Conn's syndrome (primary hyperaldosteronism) Cushing's syndrome
Drugs	Cocaine Amphetamines Ciclosporin Clonidine withdrawal Phencyclidine
Coarctation of the aorta	
Pre-eclampsia/eclampsia	

The factors that lead to the severe and rapid elevation of blood pressure in patients with malignant hypertension are poorly understood. The rapidity of onset suggests a triggering factor superimposed on pre-existing hypertension. The risks for developing malignant hypertension are related to the severity of the underlying hypertension, and therefore the role of mechanical stress on the vessel wall appears to be critical in its pathogenesis. The release of humoral vasoconstrictor substances from the stressed vessel wall is thought to be responsible for the initiation and perpetuation of the hypertensive crisis [40,41]. Increased blood pressure results in endothelial damage, with local intravascular activation of the clotting cascade, fibrinoid necrosis of small blood vessels, and release of vasoconstrictor substances [40,41]. This leads to a vicious cycle of further vascular injury, tissue ischemia, and release of vasoconstrictor substances [40,41]. The volume depletion that results from pressure natriuresis further simulates the release of vasoconstrictor substances from the kidney. The release of vasoconstrictor substances from the kidney has long been postulated to play a central role in the pathophysiology of malignant hypertension [42]. Activation of the renin–angiotensin system has been strongly implicated in the initiation and perpetuation of the vascular injury associated with malignant hypertension [29,43–45]. In addition to activation of the renin–angiotensin system, vasopressin, endothelin, and catecholamines are postulated to play important roles in the pathophysiology of hypertensive emergencies [46–49].

Clinical manifestations of hypertensive crises

The clinical manifestations of hypertensive crises are those associated with end-organ dysfunction (Table 1). Organ dysfunction is uncommon with diastolic blood pressures less than 130 mmHg (except in children and in pregnancy) [21]. However, the absolute level of blood pressure may not be as important as the rate of increase [7,50,51]. In patients with longstanding hypertension a systolic blood pressure of 200 mmHg or elevations in diastolic pressure up to 150 mmHg may be well tolerated without the development of hypertensive encephalopathy, whereas children or pregnant women may develop encephalopathy with a diastolic blood pressure of only 100 mmHg [17].

The symptoms and signs of hypertensive crises vary from patient to patient. Headache, altered level of consciousness, and/or focal neurologic signs are seen in patients with hypertensive encephalopathy [6,7]. On physical examination, these patients may have retinopathy with arteriolar changes, hemorrhages and exudates, as well as papilledema. In other patients, the cardiovascular manifestations of hypertensive crises may predominate, with angina, acute myocardial infarction, or acute left ventricular failure [9,52]. In some patients, severe injury to the kidneys may lead to acute renal failure with oliguria and/or hematuria.

In pregnant patients, the acute elevations in blood pressure may range from a mild to a life-threatening disease process. The clinical features vary but may include visual field defects, severe headaches, seizures, altered mental status, acute cerebrovascular accidents, severe right upper quadrant

abdominal pain, congestive heart failure, and oliguria. In the vast majority of cases, this process can only be terminated by delivery. The decision to continue the pregnancy or to deliver should be made following consultation between medical and obstetric personnel [18,37,53,54].

One syndrome that warrants special consideration is aortic dissection. Approximately 2000 new cases occur in the USA each year [55,56]. Aortic dissection should be considered a likely diagnostic possibility in patients presenting to the emergency department with acute chest pain and elevated blood pressure. Left untreated, about three-quarters of patients with type A dissection die within 2 weeks of an acute episode, but with successful initial therapy the 5-year survival rate increases to 75% [55,56]. Hence, timely recognition of this disease entity coupled with urgent and appropriate management is the key to a successful outcome in a majority of patients. It is important to understand that the propagation of the dissection is dependent not only on the elevation in blood pressure itself but also on the velocity of left ventricular ejection [55–58]. For this reason, the aim of antihypertensive therapy is to lessen the pulsatile load or aortic stress by lowering the blood pressure. Specific targets are the blood pressure and rate of pressure rise.

Evaluation and management of hypertensive crises

A targeted medical history and physical examination supported by appropriate laboratory evaluation is required in patients presenting with a possible hypertensive crisis [7,28]. The patient's hypertensive history and prior blood pressure control should be ascertained, as should any history of renal and cardiac disease. The use of prescribed or nonprescribed medications, and recreational drugs should be determined. The blood pressure in both arms should be measured by the physician. In obese patients appropriately sized cuffs should be used. Physical examination should include palpation of pulses in all extremities, auscultation for renal bruits, a focused neurologic examination, and a funduscopic examination.

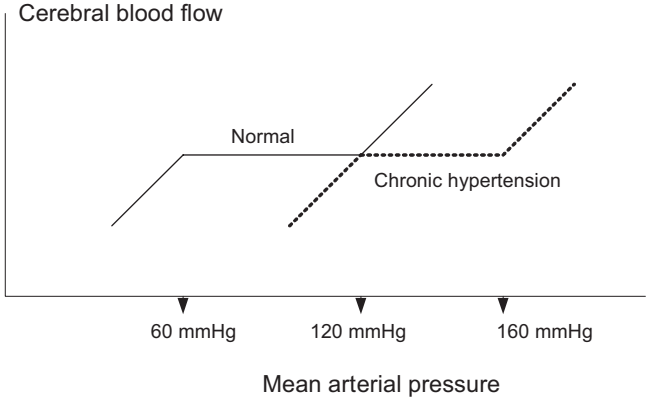
A complete blood count and smear (to exclude a microangiopathic anemia), electrolytes, blood urea nitrogen, creatinine, urinalysis, and electrocardiogram should be obtained in all patients. A chest radiograph should be obtained in patients with shortness of breath or chest pain, and a head computed tomography scan should be obtained in patients with neurologic symptoms [7,28]. In patients with unequal pulses and/or evidence of a widened mediastinum on the chest radiograph, a chest computed tomography or magnetic resonance imaging scan should be considered [55,56]. Patients in whom an aortic dissection is considered should not undergo transesophageal echocardiography until the blood pressure has been adequately controlled. One the basis of the clinical evaluation, the physician should be able to make the distinction between a hypertensive emergency/crisis and a hypertensive urgency [21].

Initial therapeutic approach

The majority of patients with severe hypertension (diastolic pressure > 109 mmHg) will have no acute end-organ damage (hypertensive urgencies). In these patients the blood pressure should be lowered gradually over a period of 24–48 hours, usually with oral medication. Rapid reduction in blood pressure in these patients may be associated with significant morbidity [59–61]. In patients with true hypertensive emergencies, rapid but controlled lowering of blood pressure is indicated to limit and prevent further organ damage [2,27,28,58,61]. However, the blood pressure should not be lowered to normal levels [3–5,11,12]. Most patients with hypertensive emergencies are chronically hypertensive and will have a rightward shift of the pressure–flow (cerebral, renal, and coronary) autoregulation curve (Fig. 1) [62]. Rapid reduction in blood pressure below the cerebral, renal, and/or coronary autoregulatory range will result in a marked reduction in organ blood flow, leading to ischemia and infarction [21]. For this reason all patients with a hypertensive emergency should be managed in an intensive care unit, where the patient can be closely monitored. Intra-arterial blood pressure monitoring may be required in patients with blood pressure that is labile and difficult to control.

A variety of different antihypertensive agents are available for use in patients with hypertensive crises. The agent(s) of choice will depend on the end-organ involved as well as the monitoring environment (Table 3). Rapid acting intravenous agents should not be used outside the intensive care unit because a precipitous and uncontrolled fall in blood pressure may have lethal consequences. Reductions in diastolic blood pressure by 10–15% or to about 110 mmHg is generally recommended. This is best achieved by an continuous infusion of a short acting, titratable, parenteral antihypertensive agent [21]. In patients with a dissecting aneurysm this goal should

Figure 1



Cerebral autoregulation in normotensive and chronically hypertensive patient.

be achieved within 5–10 min. In all other patients, this end-point should be achieved within 1 hour. Once the end-points of therapy have been reached, the patient can be started on oral maintenance therapy and the intravenous agent weaned off. It should be noted that most patients with hypertensive emergencies are volume depleted. Volume repletion with intravenous crystalloid will serve to restore organ perfusion and prevent the precipitous fall in blood pressure that may occur with antihypertensive therapy.

It should be emphasized that only patients with hypertensive emergencies require immediate reduction in markedly elevated blood pressure. In all other patients the elevated blood pressure can be lowered slowly using oral agents. Lowering the blood pressure in patients with ischemic strokes may reduce cerebral blood flow, which because of impaired autoregulation may result in further ischemic injury. The common practice of 'normalizing' blood pressure following a cerebrovascular accident is potentially dangerous. When a proximal arterial obstruction results in a mild stroke, a fall in blood pressure may result in further infarction involving the entire territory of that artery. The current recommendation of the American Heart Association is that hypertension in the setting of acute ischemic stroke should only be treated 'rarely and cautiously' [63,64]. It is generally recommended that antihypertensive therapy be reserved for patients with a diastolic pressure greater than 120–130 mmHg, aiming to reduce the pressure by no more than an arbitrary figure of 10–15% in the first 24 hours. This approach is supported by a study reported by Semplicini and colleagues [65]. Those investigators demonstrated that a higher initial blood pressure was associated with a better neurologic outcome following an acute ischemic stroke. They suggested that hypertension may be protective during an acute ischemic stroke and that lowering the blood pressure may be potentially harmful. In patients with intracerebral hematomas there is almost always a rise in intracranial pressure with reflex systemic hypertension. There is no evidence that hypertension provokes further bleeding in patients with intracranial hemorrhage. However, a precipitous fall in systemic blood pressure will compromise cerebral perfusion. The controlled lowering of the blood pressure is currently recommended only when the systolic blood pressure is greater than 200 mmHg or the diastolic pressure is greater than 110 mmHg [66–68]. This recommendation is supported by a recent study that demonstrated that the rapid decline in blood pressure within the first 24 hours after presentation was associated with increased mortality in patients with an intracranial hemorrhage [69]. The rate of decline in blood pressure was independently associated with increased mortality.

Pregnant patients with hypertensive crises represent a special group of patients. In these patients, intravenous drug therapy is reserved for those patients with systolic blood pressure persistently greater than 180 mmHg or diastolic blood pressure persistently greater than 110 mmHg (105 mmHg in some institutions) [70]. Before delivery it is desirable to maintain the diastolic blood pressure greater than 90 mmHg because this pressure allows for adequate utero-placental perfusion. If the diastolic blood pressure decreases to below 90 mmHg, then decreased uteroplacental perfusion may precipitate acute fetal distress progressing to an *in utero* death or to perinatal asphyxia [18].

Table 3

Recommended antihypertensive agents for hypertensive crises

Condition	Preferred antihypertensive agent
Acute pulmonary edema	Fenoldopam or nitroprusside in combination with nitroglycerin (up to 60 μg/min) and a loop diuretic
Acute myocardial ischemia	Labetalol or esmolol in combination with nitroglycerin (up to 60 μg/min)
Hypertensive encephalopathy	Labetalol, nicardipine, or fenoldopam
Acute aortic dissection	Labetalol or combination of nicardipine or fenoldopam and esmolol or combination of nitroprusside with either esmolol or intravenous metoprolol
Eclampsia	Labetalol or nicardipine. Hydralazine may be used in a non-ICU setting
Acute renal failure/ microangiopathic anemia	Fenoldopam or nicardipine
Sympathetic crisis/cocaine overdose	Verapamil, diltiazem, or nicardipine in combination with a benzodiazepine

ICU, intensive care unit.

Pharmacologic agents used in the treatment of hypertensive crises

The ideal pharmacologic agent for the management of hypertensive crises would be fast-acting, rapidly reversible, and titratable without significant side effects. Although no single ideal agent exists, a growing number of drugs are available for the management of hypertensive crises. The agent of choice in any particular situation will depend upon the patient's clinical presentation. The preferred agents include esmolol, labetalol, fenoldopam, and nicardipine. Phentolamine and trimethaphan camsylate are less commonly used today; however, they may be useful in particular situations such as catecholamine-induced hypertensive crises (i.e. pheochromocytoma) [3,7,27,50,51,57]. Sodium nitroprusside may be used in patients with acute pulmonary edema and/or severe left ventricular dysfunction and in patients with aortic dissection. However, because sodium nitroprusside is extremely rapid acting and a potent antihypertensive agent, intra-arterial blood pressure monitoring is required; in addition, sodium nitroprusside requires special handling to prevent its degradation by light. These factors limit the use of this drug in the emergency department [33]. Oral and sublingual nifedipine are potentially dangerous in patients with hypertensive crises and are not recommended. Clonidine and angiotensin-con-

verting enzyme inhibitors are long acting and poorly titratable, but these agents are particularly useful in the management of hypertensive urgencies [71–75]. Angiotensin-converting enzyme inhibitors are contraindicated in pregnancy [73,76]. The recommended intravenous antihypertensive agents are reviewed briefly below.

Esmolol

Esmolol is an ultra-short-acting, cardioselective, β-adrenergic blocking agent [77–79]. The onset of action of this agent is within 60 s, with a duration of action of 10–20 min [77–79]. The metabolism of esmolol is via rapid hydrolysis of ester linkages by red blood cell esterases and is not dependant upon renal or hepatic function. Because of its pharmacokinetic properties, some authors consider it an 'ideal beta-adrenergic blocker' for use in critically ill patients [21]. This agent is available for intravenous use both as a bolus and as an infusion. Esmolol is particularly useful in severe postoperative hypertension [80–86]. It is a suitable agent in situations in which the cardiac output, heart rate, and blood pressure are increased. It has proven safe in patients with acute myocardial infarction, even those who have relative contraindications to β-blockers [87]. Typically, the drug is given as a 0.5–1 mg/kg loading dose over 1 min, followed by an infusion starting at 50 μg/kg per min and increasing up to 300 μg/kg per min as necessary.

Fenoldopam

Fenoldopam has recently been approved for the management of severe hypertension in the USA. It is a dopamine agonist (DA1 agonist) that is short acting and has the advantages of increasing renal blood flow and sodium excretion [88,89]. Fenoldopam has relatively unique actions and represents a new category of antihypertensive medication. Although the structure of fenoldopam is similar to that of dopamine, fenoldopam is highly specific for only DA1 receptors and is 10 times more potent than dopamine as a renal vasodilator [90]. Fenoldopam is rapidly and extensively metabolized by conjugation in the liver, without the participation of cytochrome P450 enzymes. The onset of action is within 5 min, with the maximal response being achieved by 15 min [91–93]. The duration of action is between 30 and 60 min, with the pressure gradually returning to pretreatment values without rebound once the infusion is stopped [91–93]. No adverse effects have been reported [91]. The dose rate of fenoldopam must be individualized according to body weight and according to the desired rapidity and extent of the pharmacodynamic effect. An initial starting dose of 0.1 μg/kg per min is recommended. Fenoldopam has been demonstrated to cause a consistent dose-related decrease in blood pressure in the dose range 0.03–0.3 μg/kg per min [33]. Fenoldopam has been demonstrated to improve creatinine clearance, urine flow rates, and sodium excretion in severely hypertensive patients with both normal and impaired renal function [89,94,95]. It may therefore be the drug of choice in severely hypertensive patients with impaired renal function [96].

Labetalol

Labetalol is a combined selective α_1- and nonselective β-adrenergic receptor blocker with an α to β blocking ratio of 1 : 7 [97]. Labetalol is metabolized by the liver to form an inactive glucuronide conjugate [98]. The hypotensive effect of labetalol begins within 2–5 min after its intravenous administration, reaching a peak at 5–15 min after administration and lasting for about 2–4 hours [98,99]. Because of its β-blocking effects, the heart rate is either maintained or slightly reduced. Unlike pure β-adrenergic blocking agents, which decrease cardiac output, labetalol maintains cardiac output [100]. Labetalol reduces the systemic vascular resistance without reducing total peripheral blood flow. In addition, the cerebral, renal, and coronary blood flows are maintained [100–103]. This agent has been used in the setting of pregnancy-induced hypertensive crisis because little placental transfer occurs, mainly due to the drug's negligible lipid solubility [100].

Labetalol may be given as a loading dose of 20 mg, followed by repeated incremental doses of 20–80 mg given at 10-min intervals until the desired blood pressure is achieved. Alternatively, after the initial loading dose, an infusion commencing at 1–2 mg/min and uptitrated until the desired hypotensive effect is achieved is particularly effective. Bolus injections of 1–2 mg/kg have been reported to produce precipitous falls in blood pressure and should therefore be avoided [104].

Nicardipine

Nicardipine is a second generation dihydropyridine derivative calcium channel blocker with high vascular selectivity and strong cerebral and coronary vasodilatory activities. It is 100 times more water soluble than is nifedipine, and therefore it can be administered intravenously, making nicardipine an easily titratable intravenous calcium channel blocker [105,106]. The onset of action of intravenous nicardipine is between 5 and 15 min with a duration of action of 4–6 hours. Once administered intravenously, nicardipine crosses the blood–brain barrier and reaches the nervous tissue, where it binds to calcium-channels of the L-type, acting primarily at the level of the hippocampus [107]. Intravenous nicardipine has been shown to reduce both cardiac and cerebral ischemia [108]. The appropriate dosage of nicardipine is independent of the patient's weight, with an initial infusion rate of 5 mg/hour, increasing by 2.5 mg/hour every 5 min to a maximum of 30 mg/hour until the desired blood pressure reduction is achieved [21].

Nitroprusside

Sodium nitroprusside is an arterial and venous vasodilator that decreases both afterload and preload [109–113]. Nitroprusside decreases cerebral blood flow while increasing intracranial pressure – effects that are particularly disadvantageous in patients with hypertensive encephalopathy or following a cerebrovascular accident [114–117]. Nitroprusside is a very potent agent, with onset of action within seconds, a duration of action of 1–2 min, and a plasma half-life of

3–4 min [109–113,118]. In patients with coronary artery disease a significant reduction in regional blood flow (coronary steal) can occur [119]. In a large randomized, placebo-controlled trial, nitroprusside was shown to increase mortality when infused in the early hours after acute myocardial infarction (mortality at 13 weeks, 24.2% versus 12.7%) [120].

Nitroprusside contains 44% cyanide by weight [112]. Cyanide is released nonenzymatically from nitroprusside, the amount generated being dependent on the dose of nitroprusside administered. Cyanide is metabolized in the liver to thiocyanate [112]. Thiosulfate is required for this reaction [112,121]. Thiocyanate is 100 times less toxic than cyanide. The thiocyanate generated is excreted largely through the kidneys. Cyanide removal therefore requires adequate liver function, adequate renal function, and adequate bioavailability of thiosulfate.

Nitroprusside may cause cytotoxicity because of the release of cyanide with interference with cellular respiration [122,123]. Cyanide toxicity has been documented to result in 'unexplained cardiac arrest', coma, encephalopathy, convulsions, and irreversible focal neurologic abnormalities [113,124]. The current methods of monitoring for cyanide toxicity are insensitive. Metabolic acidosis is usually a preterminal event. In addition, a rise in serum thiocyanate levels is a late event and not directly related to cyanide toxicity. Red blood cell cyanide concentrations (although not widely available) may be a more reliable method of monitoring for cyanide toxicity [112]. A red blood cell cyanide concentration above 40 nmol/ml results in detectable metabolic changes. Levels above 200 nmol/ml are associated with severe clinical symptoms and levels greater than 400 nmol/ml are considered lethal [112]. Data suggest that nitroprusside infusion rates in excess of 4 μg/kg per min for as little as 2–3 hours may lead to cyanide levels that are within the toxic range [112]. The recommended doses of nitroprusside of up to 10 μg/kg per min result in cyanide formation at a far greater rate than human beings can detoxify. Sodium nitroprusside has also been demonstrated to cause cytotoxicity through the release of nitric oxide, with hydroxyl radical and peroxynitrite generation leading to lipid peroxidation [122,125–127].

Recently, Khot and colleagues [128] reported the use of nitroprusside in 25 normotensive patients with severe aortic stenosis and left ventricular dysfunction. After 24 hours of nitroprusside infusion (mean dose of 128 μg/min) there was a significant increase in the mean cardiac index to 2.52 ± 0.55 l/min per m^2 from a baseline value of 1.60 ± 0.35 l/min per m^2; this was associated with a significant increase in stroke volume and a significant fall in the systematic vascular resistance and pulmonary capillary wedge pressure. The nitroprusside was well tolerated, had minimal side effects, and was associated with an improvement in renal function. It should be emphasized that, in this study, the patients received the nitroprusside infusion for no longer than 24 hours and the maximum dose did not exceed 2 μg/kg per min.

Considering the potential for severe toxicity with nitroprusside, this drug should only be used when other intravenous antihypertensive agents are not available and then only in specific clinical circumstances and in patients with normal renal and hepatic function [113]. The duration of treatment should be as short as possible and the infusion rate should not exceed 2 μg/kg per min. An infusion of thiosulfate should be used in patients receiving higher dosages (4–10 μg/kg per min) of nitroprusside [121]. It has also been demonstrated that hydroxocobalamin (vitamin 12a) is safe and effective in preventing and treating cyanide toxicity associated with the use of nitroprusside. This may be given as a continuous infusion at a rate of 25 mg/hour. Hydroxocobalamin is unstable and should be stored dry and protected from light. Cyanocobalamin (vitamin B12), however, is ineffective as an antidote and is not capable of preventing cyanide toxicity.

Nifedipine, nitroglycerin, and hydralazine

Nifedipine, nitroglycerin, and hydralazine are not recommended in the management of hypertensive emergencies. The bases of these recommendations are discussed below.

Nifedipine

Nifedipine has been widely used via oral or sublingual administration in the management of hypertensive emergencies, severe hypertension associated with chronic renal failure, perioperative hypertension, and pregnancy induced hypertension [72,129–136]. Although nifedipine has been given via the sublingual route, the drug is poorly soluble and is not absorbed through the buccal mucosa. However, it is rapidly absorbed from the gastrointestinal tract after the capsule is broken/dissolved [137]. This mode of administration has not been approved by the US Food and Drug Administration. A significant decrease in blood pressure is usually observed 5–10 min after nifedipine administration, with a peak effect at between 30 and 60 min and a duration of action of approximately 6–8 hours [129].

Sudden uncontrolled and severe reductions in blood pressure accompanying the administration of nifedipine may precipitate cerebral, renal, and myocardial ischemic events, which have been associated with fatal outcomes [72,108,130–133,137–140]. Elderly hypertensive patients with underlying organ impairment and structural vascular disease are more vulnerable to the rapid and uncontrolled reduction in arterial pressure [138]. Given the seriousness of the reported adverse events and the lack of any clinical documentation attesting to a benefit, the use of nifedipine capsules for hypertensive emergencies and 'pseudo-emergencies' should be abandoned [138]. The Cardiorenal Advisory Committee of the US Food and Drug Administration has concluded that the practice of administering sublingual/oral nifedipine should be abandoned because this agent is neither safe nor efficacious [141].

Nitroglycerin, hydralazine, and diuretics

Nitroglycerin is a potent venodilator, and only at high doses does it affect arterial tone [142]. It causes hypotension and reflex tachycardia, which are exacerbated by the volume depletion characteristic of hypertensive emergencies. Nitroglycerin reduces blood pressure by reducing preload and cardiac output, which are undesirable effects in patients with compromised cerebral and renal perfusion. Low dose (60 mg/min) nitroglycerin may, however, be used as an adjunct to intravenous antihypertensive therapy in patients with hypertensive emergencies associated with acute coronary syndromes or acute pulmonary edema.

Hydralazine is a direct acting vasodilator. Following intramuscular or intravenous administration there is an initial latency period of 5–15 min followed by a progressive and often precipitous fall in blood pressure that can last up to 12 hours [143,144]. Although hydralazine's circulating half-life is only about 3 hours, the half-time of its effect on blood pressure is about 100 hours [145–148]. Because of hydralazine's prolonged and unpredictable antihypertensive effects and the inability to titrate the drug's hypotensive effect effectively, hydralazine is best avoided in the management of hypertensive crises.

Volume depletion is common in patients with malignant hypertension, and the administration of a diuretic together with a hypertensive agent can lead to a precipitous drop in blood pressure. Diuretics should be avoided unless specifically indicated for volume overload as occurs in renal parenchymal disease or coexisting pulmonary edema.

Conclusion

Patients with hypertensive crises may require immediate reduction in elevated blood pressure to prevent and arrest progressive end-organ damage. The best clinical setting in which to achieve this blood pressure control is in the intensive care unit, with the use of titratable intravenous hypotensive agents. There are several antihypertensive agents available for this purpose, including esmolol, nicardipine, labetalol, and fenoldopam. Although sodium nitroprusside is a rapid acting and potent antihypertensive agents, it may be associated with significant toxicity and should therefore only be used in select circumstances and at a dose that should not exceed 2 μg/kg per min. The appropriate therapeutic approach in each patient will depend on the clinical presentation. Agents such as nifedipine and hydralazine should be abandoned because these agents are associated with significant toxicities and/or side effects.

Competing interests

None declared.

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