HYPERTENSIVE CRISIS: HYPERTENSIVE EMERGENCIES AND URGENCIES

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ABSTRACT

Hypertension affects an estimated 50 million people in the United States, and it contributed to more than 250,000 deaths in the year 2000 because of end-organ damage. Normal blood pressure is defined as a systolic blood pressure of less than 120 mm Hg and diastolic blood pressure of less than 80 mm Hg. Hypertension is defined as a sys- tolic blood pressure of 140 mm Hg or higher or a diastolic blood pressure of 90 mm Hg or higher. A systolic blood pressure of 120 to 139 mm Hg or a diastolic blood pressure of 80 to 89 mm Hg is considered prehypertension, because people in this range of blood pressure have higher tendency to develop hypertension over time. There is a con- tinuous, graded relationship between hypertension and cardiovascular risk; even a slightly elevated blood pressure increases risk for cardiovascular disease. The maximum blood pressure as well as the duration of elevated pressure determines the outcome. Most patients who have chronically uncontrolled hypertension suffer end-organ dam- age over time. Patients with previously untreated or inadequately treated high blood pressures are most prone to acute rises in their blood pressures. Patients with secondary causes of hypertension are at higher risk of acute rises of blood pressure than patients who have essential hypertension. The terms ‘‘malignant hypertension, ‘hypertensive emergency,’’ and ‘‘hypertensive urgency’’ were instituted to describe these acute rises in blood pressure and resulting end-organ damage. Hypertensive crisis includes hypertensive emer- gencies and urgencies. Hypertensive emergency is defined as severe hypertension with acute end- organ damage, such as aortic dissection, heart failure, papilledema, or stroke. Although there is no blood pressure threshold for the diagnosis of hypertensive emergency, most end-organ damage is noted with diastolic blood pressures exceeding 120 to 130 mm Hg. In these patients, immediate but monitored reduction, often accomplished with parenteral medications, is essential in preventing long-term damage. Hypertensive urgency, on the other hand, describes significantly elevated blood pressure but without evidence of acute end-organ damage. These patients also need reductions in their blood pressures; but these reductions can be achieved over a period of days, with oral medi- cations and usually without an intensive monitoring setting.

Keywords: hypertensive, emergencies, urgencies

INTRODUCTION

Physicians have noticed the effects of hyper- tension and hypertensive crises for decades. Vol- hard and Fahr [8] were the first to notice the acute changes in blood pressure and the differences in pathophysiology of these changes from the chronically elevated blood pressure. They noted that patients who had severe hypertension had fundoscopic changes such as retinopathy and papille- dema along with renal insufficiency and fibroid necrosis of the renal arterioles. Also, they noticed that patients who had acute elevations in blood pressure were more prone to papilledema and to acute changes in their kidneys. In 1914, they defined the term ‘‘malignant hypertension’’ as an el- evation in blood pressure with the sign of acute end organ damage. Subsequently, in 1921, Keith and Wagener described a similar finding of papilledema and severe retinopathy in patients who had severe hypertension but who did not have renal insufficiency. They then realized that the end-organ eye and kidney damage were not mutually exclusive to acute hypertensive episodes and therefore broadened the definition of malignant hypertension by stating that renal insufficiency was not a necessary

requirement for acute hypertensive damage. Keith and Wagener [9] also used the term ‘‘accelerated hypertension,’’ which they defined as a syndrome with severe elevations in blood pressure in the presence of retinal hemorrhages and exudates but without papilledema. Later studies have shown that retinal hemorrhages and exudates are important in malignant hypertension and are associated with decreased survival. Notably, however, the presence or absence of papilledema is not associated with decreased survival [10,11].

In 1928, Oppenheimer and Fishberg [12] were the first to use the term ‘‘hypertensive encephalop- athy’’ when they noted malignant hypertension associated with headaches, convulsions, and neu- rologic deficits in a 19-year-old student. Currently, the terms ‘‘malignant hypertension’’ and ‘‘acceler- ated hypertension’’ are used infrequently and have been replaced by terms such as ‘‘hypertensive crisis,’’ ‘‘hypertensive emergency,’’ and ‘‘hypertensive urgency.

The prevalence of hypertension has increased, partially because of the stringent definition of hypertension. There are notable demographic trends in the prevalence of hypertension. Hyper- tension is more common in older age groups and is more common in men than in women [13]. It is 1.5 to two times more prevalent in black Americans. An analysis of data from the 1999 to 2000 National Health and Nutrition Examination Survey has shown that the combined prevalence of prehypertension and hypertension has increased to 60% of American adults (67% of men and 50% of women), and 27% of American adults have established hypertension. The combined prevalence of prehypertension and hypertension is 40% in the 18- to 39-years age group and is 88% in the greater than 60 years age group [14]. This survey showed certain risk predictors of hypertension. Education level was a notable factor. The combined prevalence of prehypertension and hypertension in creased from 54% in the high school educated group to 65% in the non–high-school–educated group. Obesity was also an important risk predictor in this analysis; 75% of overweight individuals were prehypertensive or hypertensive, but only 47% of the nonoverweight group qualified as such.

Patients who were noted to have prehypertension were also noted to have other risk factors for stroke and cardiovascular disease, such as hyper- cholesterolemia, obesity, and diabetes. These risk factors were less prevalent in people who had normal blood pressures. The percentage of people who had more than one risk factor for cardiovascular disease was higher in the prehypertensive group than in patients who had normal blood pressure [14]. This cross-sectional analysis also evaluated patients who, when made aware of their hypertension, followed dietary, lifestyle, and medication changes. It was noted that 7% of patients did not adopt any lifestyle changes, and 15% of patients would not take any antihypertensive medications. The problem was more notable in younger patients and in Mexican-American patients. Of the patients taking anti-hypertensive medications, 54% had their hypertension con- trolled. Men and patients with higher education were more likely to have their blood pressures well controlled.

Of the estimated 50 million Americans with hypertension, less than 1% will have a hypertensive crisis [15]. In a study by Zampaglione and as sociates [16], hypertensive crises were found to account for more than 25% of all patient visits to a medical section of an emergency department. One third of those patients were noted to have hypertensive emergencies. In the years when treatment of hypertensive crises was difficult, be- cause of inadequate monitoring and lack of parenteral medications, survival was only 20% at 1 year and 1% at 5 years [17]. Before antihypertensive agents became available, thoracolumbar sympathectomy prolonged survival to 40% at 6.5 years. With the advent of ganglionic blocking medications, the 5-year survival rates increased to 50% to 60% in 1960 [18]. During the past 2 decades, with the increased focus on blood pressure control and emphasis on compliance, the 10-year survival rates have approached 70% [19].

Cause

Ninety five per cent of patients who have hypertension have no obvious underlying cause. As such, hypertension without secondary causes is defined as essential hypertension. The remaining 5% of patients have an underlying cause for their elevated blood pressures, of which certain groups have higher chances of presenting with a hypertensive crisis (Box 1). Use of recreational drugs, such as cocaine, has become a frequent cause of hypertensive crisis. Cocaine amphetamines, phencyclidine hydrochloride, and diet pills are sympa- thomimetic and thus may cause severe acute hypertension. Patients taking monoamine oxidase inhibitors along with tricyclic antidepressants, antihistamines, or food with tyramine are prone to hypertensive crises. Withdrawal syndromes from drugs such as clonidine or beta-blockers may also precipitate hypertensive crises [20]. Pheochromocytoma is a rare cause of hypertensive crises. Patients with spinal cord disorders, such as Guillain Barre´syndrome, are also at a higher risk for hypertensive crises. These patients are prone to autonomic overactivity syndrome manifested by severe hypertension, bradycardia, headache, and diaphoresis. The syndrome is triggered by stimulation of dermatomes or muscles innervated by nerves below the spinal cord lesions.

Pathophysiology

Normal mechanisms to regulate blood pressure

Blood pressure regulation is a critical action that allows perfusion to vital organs of the body. This action is based on a balance between pe- ripheral vascular resistance and cardiac output and is dependent on the integrated actions of the cardiovascular, renal, neural, and endocrine systems. This interdependence allows a back-up system so that the body can cope with internal and external stresses such as thirst, fear, infection, and trauma. Multiple intrinsic systems are activated in the body in response to external and internal stressors [21]. The renin angiotensin aldosterone system is thought to be critically responsible for blood pressure changes. Renin is released from the juxtaglomerular apparatus in response to low sodium intake, underperfusion of the kidney, and increased sympathetic activity. Renin is responsi- ble for converting angiotensinogen to angiotensin, which is not metabolically active. The angiotensin is subsequently converted to angiotensin II in the lungs by the angiotensin-converting enzyme. An- giotensin II is a potent vasoconstrictor, which leads to increases in blood pressure. Besides its intrinsic vasoconstrictive effects, angiotensin II also causes aldosterone release, which further increases blood pressure by causing salt and water retention. Stud- ies in rats support the role of the renin-angiotensin- aldosterone system in blood pressure elevation. When rats were given the Ren-2 gene, which activates the renin-angiotensin-aldosterone system, they developed severe hypertension [22]. Fur ther support comes from therapeutic methods, such as using angiotensin-converting enzyme inhibitors or angiotensin receptor blockers or surgical removal of an ischemic kidney, which can prevent blood pressure elevations [23].

The renin-angiotensin-aldosterone system is not considered solely responsible for changes in blood pressure. Black Americans, for instance, often have low renin, angiotensin II, and aldoste- rone levels and yet have a notably higher incidence of hypertension. Therefore, they are less responsive to medications blocking the renin-angiotensin- aldosterone system. Theoretically, patients who have low renin states might have noncirculatory local renin-angiotensin paracrine or epicrine sys- tems. These systems have been found in the kidney, arterial tree, and the heart; and are probably responsible

for local control of blood pressure [24]. The sympathetic nervous system also affects blood pressure, especially in times of stress and exercise. The sympathetic nervous system can cause arterial vasoconstriction and can raise car- diac output. It is thought that initially the sympa- thetic nervous system increases the cardiac output without affecting peripheral vascular resistance. The raised cardiac output increases flow to the vascular bed, and as the cardiac output increases, the autoregulatory response of the vascular bed is activated. This autoregulatory response results in constriction of the arterioles to prevent the pressure from reaching the capillaries and affecting cell hemostasis [21].

In addition, endothelial function plays a central role in blood pressure maintenance. The endothe- lium secretes nitric oxide, prostacylin, and endothelin, which modulate vascular tone. Nitric oxide is released by endothelial agonists such as acetylcholine and norepinephrine and in response to shear stress [21]. Endothelin-1 has great vasocon- strictive activities and may cause a saltsensitive rise in blood pressure and a rise in blood pressure by triggering the renin-angiotensin-aldosterone system [24]. Other vasoactive substances involved in blood pressure maintenance include bradykinin and natriuretic peptides. Bradykinin is a potent vasodilator that is inactivated by angiotensin-converting enzyme. Natriuretic peptides are se- creted from the heart in response to increase in blood volume and cause an increase in sodium and water excretion.

Altered mechanisms in hypertension and hypertensive crises

The pathophysiology of hypertensive crisis is not well understood. It is thought that an abrupt rise in blood pressure, possibly secondary to a known or unknown stimulus, may trigger the event. During this abrupt initial rise in blood pressure, the endothelium tries to compensate for the change in vasoreactivity by releasing nitric oxide. When the larger arteries and arterioles sense elevated blood pressures, they respond with vasoconstriction and subsequently with hy- pertrophy to limit pressure reaching the cellular level and affecting cellular activity. Prolonged smooth muscle contraction leads to endothelial dysfunction, loss of nitric oxide production, and irreversible rise in peripheral arterial resistance. Without the continuous release of nitric oxide, the hypertensive response becomes more severe, promoting further endothelial damage, and a vicious cycle continues. The endothelial dysfunction is further triggered by inflammation induced by mechanical stretch. The expression of inflammatory markers such as cytokines, endothelial adhe- sion molecules, and endothelin-1 is increased [25,26]. These molecular events probably increase the endothelial permeability, inhibit fibrinolysis, and, as a result, activate coagulation. Coagulation along with platelet adhesion and aggregation results in deposition of fibrinoid material, increased inflammation, and the vasoconstriction of the arteries, resulting in further endothelial dysfunction. The role of the renin-angiotensin-aldosterone system also seems to be important in hypertensive emergency. There seems to be an amplification of this system that contributes to vascular injury and tissue ischemia [27].

The blood pressure at which the acute end- organ damage starts occurring is different in each individual. Patients who are more chronically hypertensive have had more smooth muscle con- traction and subsequent arterial hypertrophy, which lessens the effect of acute rise in blood pressure on the capillary circulation. Although malignant hypertension is defined as a diastolic blood pressure

greater than 130 mm Hg, normotensive patients who have not had time to establish compensatory autoregulatory mechanisms are more sensitive to elevations in blood pressure and may suffer end-organ damage when diastolic blood pressure becomes greater than 100 mm Hg.

Clinical manifestations

Hypertensive crisis shares all of the pathologic mechanisms and end-organ complications of the milder forms of hypertension [27]. In one study of the prevalence of end-organ complications in hypertensive crisis, central nervous system abnor- malities were the most frequent. Cerebral infarctions were noted in 24%, encephalopathy in 16%, and intracerebral or subarachnoid hemorrhage in 4% of patients. Central nervous system abnormalities were followed in incidence by car- diovascular complications such as acute heart fail- ure or pulmonary edema, which were seen in 36% of patients, and acute myocardial infarction or unstable angina in 12% of patients. Aortic dissec- tion was noted in 2%, and eclampsia was noted in 4.5% of patients [16]. The endorgan damage is outlined in Box 2.

Acute neurologic syndromes

The cerebral vasculature must maintain a constant cerebral perfusion despite changes in blood pressure. Cerebral autoregulation is the inherent ability of the cerebral vasculature to maintain this constant cerebral blood flow [28,29]. Normotensive people maintain a constant cerebral blood flow between mean arterial pressures of 60 mm Hg and 120 mm Hg. As the mean arterial pressure increases, there is disruption of the cerebral endo- thelium and interruption of the blood brain barrier. Fibrinoid material deposits in the cerebral vasculature and causes narrowing of the vascular lumen. The cerebral vasculature, in turn, attempts to vasodilate around the narrowed lumen, which leads to cerebral edema and microhemorrhages [30]. The changes in cerebral vasculature and cere- bral perfusion seem to affect primarily the white matter in the parieto-occipital areas of the brain [31]. The predilection toward the parieto-occipital regions possibly results from decreased sympathetic innervation of the vessels in this region [32]. There are also reports of brainstem involvement, however [33].

Normotensive patients may develop endothe- lial dysfunction at lower mean arterial pressures, whereas chronically hypertensive patients can tolerate higher mean arterial pressures before they develop such a dysfunction. Chronically hypertensive patients have the capacity to autoregulate and have cerebral blood flow and oxygen consumption similar to those in normotensive persons [34]. Changes in the structure of the arte- rial wall cause increased stiffness and higher cerebrovascular resistance, however [35]. Although a higher threshold must be reached before they have disruption of their autoregulation system, hypertensive patients, because of the increased cerebrovascular resistance, are more prone to cere- bral ischemia when flow decreases [30].

Hypertensive encephalopathy is one of the clinical manifestations of cerebral edema and microhemorrhages seen with dysfunction of cerebral autoregulation. It is defined as an acute organic brain syndrome or delirium in the setting of severe hypertension. Symptoms include severe headache, nausea, vomiting, visual disturbances, confusion, and focal or generalized weakness. Signs include

disorientation, focal neurologic defects, focal or generalized seizures, and nystagmus. If not adequately treated, hypertensive encephalopathy can lead to cerebral hemorrhage, coma, and death, but with proper treatment it is completely reversible [36]. The diagnosis of hypertensive encephalopathy is a clinical diagnosis. Stroke, sub- arachnoid hemorrhage, mass lesions, seizure disorder, and vasculitides need to be ruled out.

Cerebral infarction, caused by an imbalance between supply and demand, is another neurologic sequela of severe acute rises in blood pressure [37]. Intracranial and subarachnoid hemorrhages are other possible neurologic complications of hypertensive crisis. The risk is increased in patients who have intracranial aneurysms and in those taking anticoagulant medications.

Myocardial ischemia

Hypertension affects the structure and function of the coronary vasculature and left ventricle. Activation of the renin-angiotensin-aldosterone system in hypertension constricts systemic vasculature and, thereby, increases myocardial oxygen demand by increasing left ventricular wall tension. Increasing wall tension leads to hypertrophy of the left ventricular myocytes and to deposition of protein and collagen in the extracellular matrix of the ventricular wall. These actions increase ventricular mass, which further increases oxygen demand on the heart. A second effect of the hypertrophy is that the newly thickened ventricle can cause coronary compression and decreased luminal blood flow. Thirdly, hypertension can increase the epicardial coronary wall thickness, which increases the wall to lumen ratio and de- creases coronary blood flow reserve. Concomitant atherosclerosis worsens the wall-to-lumen ratio, further decreases coronary flow reserve, and leads to coronary ischemia [38]. Acute rise in blood pressure also results in endothelial injury at the level of the coronary capillaries.

Left ventricular failure

Another effect of hypertensive crisis on the heart is left ventricular failure and acute pulmonary edema. In certain cases, despite increasing wall tension, the left ventricle cannot hypertrophy enough to overcome the acute rise in systemic vascular resistance. This inability to compensate leads to left ventricular failure and a backup of flow causing pulmonary edema. Secondly, neurohormonal activation of the renin angiotensin aldosterone system leads to increased sodium content and increased total body water. In addition, left ventricular hypertrophy leads to focal ischemia and subsequent inadequate diastolic filling, which can result in imbalance between left ventricular contraction and relaxation, leading to pulmonary edema [5]. Clinically, patients show signs of volume overload or signs of reduced tis- sue perfusion such as cool limbs.

Aortic dissection

Aortic dissection is the most rapidly fatal complication of hypertensive crises. Risk factors for dissection include untreated hypertension, advanced age, and diseases of the aortic wall. Dilation of the aorta caused by atherosclerosis and high blood pressures tear the intima of the vessel, allowing a surge of blood into the aortic wall. The blood driven by pulsatile pressure separates the arterial wall into two layers [39]. Clinically, patients complain of retrosternal or interscapular chest pain that

migrates to the back. If dissection extends proximally, it can lead to aortic insufficiency or a pericardial effusion. Dissection can lead to compression or occlusion of a branch of the aorta and subsequently lead to organ ischemia. Clinical signs that are notable with dissection include discrepancies between pulses, murmur of aortic insufficiency, and neurologic deficits [40]. Diagnosis of aortic dissection can be confirmed with transesophageal echocardiography, CT, or MRI [41].

Hypertensive retinopathy

Retinopathy was one of the first signs of hypertension, noted in 1914. In the early years fundoscopy was considered a definitive tool in diagnosing hypertensive encephalopathy. Papilledema was noted in patients who had hypertensive encephalopathy but was not necessary for diagnosis [42]. Retinal hemorrhages and exudates were considered indicative of malignant hypertension. Since 1914, multiple studies have looked at retinopathy in the setting of hypertension. In mild to moderate hypertension, the degree of focal narrowing of arterioles has been associated with the level of blood pressure rise. No relationship has been found between retinal changes and the end-organ damages such as ventricular hypertrophy or microalbuminuria, however [43]. Ophthalmoscopy may be useful in recognizing acute hypertensive targetorgan damage such as hyper- tensive encephalopathy, but the absence of retinal exudates, hemorrhages, or papilledema does not exclude the diagnosis [11].

Acute renal insufficiency

Acute renal insufficiency may be a cause or result of rapidly progressive hypertension. Important causes of hypertension are parenchymal disease, such as acute glomerulonephritis or renal artery stenosis, or cyclosporine use in kidney transplant patients. Renal insufficiency could also be a result of hypertension and hypertensive crisis, however. Normal renal autoregulation enables the kidney to maintain a constant renal blood flow and glomerular filtration rate for mean arterial pres- sures between 80 and 160 mm Hg. Under normal conditions, autoregulatory vasodilation is maxi- mal at a mean arterial pressure of about 80 mm Hg. In chronic hypertension, the small arteries of the kidney, including the afferent arteriole, undergo pathologic changes that alter renal autoregulation, showing signs of endothelial dysfunction and impaired vasodilation. Structural changes initially are probably protective of the kidney, but over time progressive narrowing of the preglomerular vessels results in ischemic injury, tubular atrophy, and fibrosis. With the impairment of the renal autoregulatory system, the intraglomerular pres- sure begins to vary directly with systemic arterial pressure [44]. As such, the afferent vasculature be- comes a passive conduit and cannot prevent the kidney from being affected by fluctuations in pres- sure and flow, leading to acute renal ischemia in cases of hypertensive crisis.

Pregnancy-induced hypertension

Preeclampsia is characterized as a syndrome of pregnancy-induced hypertension, edema, and proteinuria in a pregnant woman after the twentieth week of gestation [27]. Eclampsia is the end result of this spectrum and is associated with acute hyper- tension, edema, proteinuria, and concomitant seizures. Although the pathophysiologic mechanisms of preeclampsia and eclampsia are not well

under- stood, blood pressure elevation is characterized by an increased responsiveness to vasoconstrictors, especially angiotensin II. There is also decreased sensitivity to endothelium-derived vasodilators [27]. Pregnancy-induced hypertension usually re- solves spontaneously after delivery of baby.

Postoperative hypertension

The postoperative hypertensive crisis is classically an acute rise in blood pressure within the first 2 hours after surgery and is typically short in duration, with most patients requiring treatment for 6 hours or less [45]. Although postoperative hypertensive crises can occur with any surgery, they are more common with cardiothoracic, vascular, head, neck, and neurosurgical procedures [45]. In one study of patients undergoing radical neck dissection, the frequency of hypertensive crisis ranged from 9% to 25% [46]. A feared complication of postoperative hypertensive crisis is bleeding from operation site [47]. The pathophysiology of postoperative hypertensive crisis is probably related to stimulation of the sympathetic nervous system and catecholamine surge [48].

Clinical evaluation

History and detailed physical examination are important in all patients who present with severe hypertension. A thorough history is important to determine the time since diagnosis of hypertension, the severity, and the baseline blood pressures at home. Determining the presence of end-organ damage and other comorbidities is important, because both are crucial factors influencing the choice of antihypertensive drugs. Knowledge of the patient's medications and compliance with these medications, including over-the-counter medications and recreational drugs, is essential, because both could contribute to an acute rise in blood pressure. Blood pressure should be checked in both arms and should be done in supine and standing positions, if possible, to determine volume status. Neurologic examination is important to determine the focal signs of an ischemic or hemorrhagic stroke. The presence of delirium, nausea, vomiting, and seizures suggests hypertensive encephalopathy. Fundoscopic examination could be of help, because the presence of exudates, hemorrhage, or papilledema supports the diagnosis of hypertensive encephalopathy. Cardiovascular examination includes listening for new murmurs of aortic in- sufficiency associated with dissection or of ischemic mitral regurgitation. A gallop or left ventricular heave could suggest heart failure. Crackles in the lung fields suggest pulmonary edema. Laboratory studies should include serum electrolytes, blood urea nitrogen, serum creatinine level, blood cell count, and peripheral smear. An ECG should be taken for myocardial ischemia and left ventricular hypertrophy, and a chest radiograph should be obtained for cardiac enlargement and widened mediastinum. Urine analysis is indicated for as- sessment of proteinuria and tubular casts. Plasma renin and aldosterone levels could be obtained if patient is not taking diuretics or other medications that could have affected these levels [22].

Treatment

Hypertensive urgency can be treated in a non- ICU setting with oral medications over 24 to 48 hours. Medications such as beta-blockers, diu- retics, angiotensin-converting enzyme inhibitors, and calcium-channel blockers can be titrated initially as an inpatient; then the patient can be

discharged with close follow-up. If there is acute end-organ damage, however, the patient should be admitted to the ICU and treated with in- travenous medications. The goal of therapy is prompt but gradual reduction in blood pressure. The most reasonable goal is to lower the mean arterial pressure by about 25% or to reduce the diastolic blood pressure to 100 to 110 mm Hg.

Medication options for treatment

There have been no large clinical trials to determine the optimal pharmacologic therapy in hypertensive emergency patients, primarily because of the heterogeneity among the patients and their end-organ damage. As such, manage- ment of hypertensive crisis should be dictated by individual presentation and should be specific to the end organ at risk.

Sodium nitroprusside is the drug of choice for most hypertensive emergencies because it has an immediate onset of action and can be titrated quickly and accurately. The duration of effect is 1 to 2 minutes. The mechanism of action of this agent is probably similar to that of endogenous nitric oxide. Sodium nitroprusside is an endoge- nous arteriolar and venous dilator and has no effects on the autonomic or central nervous system [49]. The venous dilation decreases preload to the heart and subsequently decreases cardiac output, whereas the arterial dilation inhibits the reflex rise in blood pressure from the drop in cardiac output. Because sodium nitroprusside is a direct vasodila- tor, one might think that it increases cerebral blood flow and intracranial pressure. The fall in systemic pressure, however, seems to inhibit the rise in cere- bral blood flow, and patients who have neurologic damage respond well to this agent [18]. Sodium ni- troprusside must be administered as an infusion and thus requires continuous surveillance with in- tra-arterial monitoring. An end product of nitro- prusside is thiocyanate, a precursor to cyanide that can causes nausea, vomiting, lactic acidosis, and altered mental status. Cyanide toxicity can be rapidly fatal. Sodium nitroprusside is broken down by the liver and cleared through the kidney, and thus thiocyanate levels must be followed in patients who have hepatic or renal insufficiency to ensure prevention of a toxic buildup [21].

Labetalol is another first-line agent for hyper- tensive emergency. It is a combined alpha- and beta-blocking agent; the beta-blocking activity of labetalol is five- to tenfold that of the alpha component [50]. The beta effects of labetalol are only about one fifth the activity of propranolol, however [18]. Its onset of action is within 5 to 10 minutes, and the duration of action is about 3 to 6 hours. Labetalol can be used safely in most patients, but caution should be exercised in patients who have severe bradycardia, congestive heart failure, or bronchospasm.

Fenoldopam is the first selective dopamine-1 receptor agonist approved for in-hospital shorter- term management of severe hypertension up to the first 48 hours of treatment [51–54]. The mech- anism of action involves activating dopamine at the level of the kidney. Dopamine is a well-known vasoconstrictor and is sympathomimetic at inter- mediate to high doses. At low doses, however, do- pamine lowers diastolic blood pressure and, importantly, increases renal perfusion and pro- motes diuresis. Fenoldopam is administered by parenteral continuous infusion and has 50% of its maximal effect within 15 minutes. Its duration of action is about 10 to 15 minutes; thus, it can be discontinued swiftly if the decrease in blood pres- sure is too rapid. The efficacy of fenoldopam in re- nal perfusion is equal to or possibly better than that of sodium nitroprusside. There are no toxic metabolites of fenoldopam; however, the onset of action is slower, and the duration of effect is

longer than that of sodium nitroprusside. Patients develop tachyphylaxis to fenoldopam after 48 hours, and headache can be a side effect.

Nicardipine is a calcium-channel blocker ad- ministered parenterally by continuous infusion for hypertensive crises. The onset of action of this drug is 5 to 10 minutes, and the duration of action is 1 to 4 hours. Adverse reactions are reflex tachycardia and headache [55]. Nicardipine is contraindicated in patients who have heart failure.

Esmolol is a cardioselective beta-blocker with a short duration of action. It reduces the systolic blood pressure and mean arterial pressure as well as heart rate, cardiac output, and stroke volume. There is a notable decrease in myocardial oxygen consumption. Peak effects are generally seen within 6 to 10 minutes after a bolus dose. The effects resolve 20 minutes after discontinuation of infusion. The elimination half-life of esmolol is about 8 minutes.

Choice of agent

The choice of pharmacologic agent to treat hypertensive crisis should be tailored to each individual based on risks, comorbidities, and the end-organ damage. The lower limit of cerebral blood flow autoregulation is reached when blood pressure is reduced by 25%, and the cerebral ischemia can be precipitated with rapid reductions of blood pressure of greater than 50% [35]. Hence, rates with reduction of blood pressure, therapy should be suspended, and blood pressure should be allowed to rise. Blood pressure usually declines spontaneously to prestroke levels within 4 days of an acute ischemic stroke without any antihyper- tensive treatments [37]. Sodium nitroprusside is the drug of choice for treatment of acute neuro- logic syndromes in hypertensive crisis. Labetolol is a good alternative unless there is evidence of severe bradycardia associated with the cerebral edema. Clonidine and methyldopa should not be used, because they can cause central nervous system depression and complicate the clinical picture.

Severe acute hypertension often results in myocardial ischemia even with patent coronary arteries. In this situation, intravenous nitroglyc- erin is effective in reducing systemic vascular resistance and improving coronary perfusion. Nitrates should be given until symptoms subside or until diastolic blood pressure is 100 mm Hg. Beta-blockers and calcium-channel blockers are also potential options; both can decrease blood pressure while improving myocardial oxygena- tion. Calcium-channel blockers should be used with caution in patients who have possible heart failure. Acute pulmonary edema that is precipi- tated by hypertension is best treated with sodium nitroprusside. The concomitant venous and arte- rial dilation improve forward flow and cardiac output. This agent should be used in conjunction with morphine, oxygen, and a loop diuretic [49].

Treatment of an aortic dissection depends on location of the injury [41]. Type A or proximal aortic dissections need immediate institution of antihypertensive medications and immediate sur- gery, but type B or distal aorta dissections can be controlled medically. The medical therapy of aortic dissection is aimed at reducing the shear stress on aortic wall. This reduction is achieved by lowering diastolic blood pressure to less than 100 to 110 mm Hg and by decreasing heart rate. This reduction is best achieved with a combination of an intravenous beta-blocker and sodium nitro- prusside to decrease both the blood pressure and the heart rate. Another option is the use of labeto- lol, which has both alpha- and beta-blocking effects.

Renal insufficiency is a cause and a conse- quence of severe hypertension. These patients need reduction of systemic vascular resistance without compromising renal blood flow or glo- merular filtration rate. Fenoldopam is a good choice in these patients because of the improve- ment in renal perfusion, diuresis, and lack of production of toxic metabolites. Tolerance does develop to fenoldopam after 48 hours [53]. Sodi- um nitroprusside can also be used, but there is a risk of thiocyanate toxicity, and the thiocyanate level needs to be closely monitored. Calcium- channel blockers are effective and well tolerated in renal transplant patients. Beta-blockers are also useful agents in hypertension in kidney dis- ease. Calcium-channel blockers and beta-blockers have no clinically important effects on glomerular filtration or renal hemodynamics [44]. Patients who have renal insufficiency should not be treated with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers.

In pre-eclampsia and eclampsia, blood pressure control is essential. Many of the traditional anti- hypertensive medications are contraindicated in pregnancy because of their detrimental effects on the fetus. Angiotensin-converting enzyme inhibi- tors and angiotensin receptor blockers can ad- versely affect fetal development and increase fetal morbidity. Calcium-channel blockers reduce blood pressure but decrease uterine blood flow and can inhibit labor. Methyldopa is the mainstay of treatment of blood pressure in pregnant patients. It works centrally in reducing blood pressure and heart rate. Methyldopa can be administered orally or intravenously. With renal dysfunction the doses need to be adjusted. The side effects are drowsi- ness, fever, and jaundice. The medication does cross into the placenta but is considered class B in pregnancy [2]. Hydralazine is another agent that is safe in pregnancy and can be administered safely parenterally. Hydralazine may cause reflex tachy- cardia and fluid retention because it activates the renin-angiotensin-aldosterone system [27]. Data show that labetolol is probably effective in reduc- ing blood pressure in treatment of eclampsia with- out inducing fetal distress [56].

Pheochromocytoma is a rare cause of parox- ysmal or sustained blood pressure and can induce hypertensive crisis. The treatment of choice in these patients is labetolol or phentolamine (an alpha-blocking agent). It is important not to use beta-blockers alone, because then there is an unopposed alpha activity that will worsen the vasoconstriction, resulting in a further increase in blood pressure. A reflex hypertensive crisis can develop in patients who have abruptly stopped taking antihypertensives, particularly clonidine or beta-blockers. The treatment in these cases is to restart previous medications after the initial reduction of blood pressure with labetolol or sodium nitroprusside. Postoperative hypertension is typically related to catecholamine surge from activation of the sympathetic nervous system. Therefore, the treatment of choice for postopera- tive hypertensive crisis is with a beta-blocker or labetolol.

CONCLUSION

Hypertensive crisis is a serious condition that is associated with end-organ damage or may result in end-organ damage if left untreated. Causes of acute rises in blood pressure include medications, noncompliance, and poorly controlled chronic hypertension. Treatment of a hypertensive crisis should be tailored to each individual based on the extent of end-organ injury and comorbid condi-

tions. Prompt and rapid reduction of blood pressure under continuous surveillance is essential in patients who have acute end-organ damage.

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