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Abstract

As hypertension becomes more prevalent in the pediatric population, clinicians are more likely to encounter hypertensive emergencies in children, which require pharmacists and physicians to be educated on the therapeutic options for these emergencies. However, the strict governmental requirements on the testing of these drugs in pediatric patients have limited the amount of available evidence on which to base clinical decisions. This review will highlight the available evidence and preferred treatment options for the management of pediatric hypertensive emergencies.

Introduction

Historically only a disease of adults, hypertension is increasing in the pediatric population. Recent studies show that the prevalence of hypertension in school-age children is about 4-5 percent.[1] In children, hypertension is defined as systolic blood pressure and/or diastolic blood pressure greater than the 95th percentile for sex, age and height on at least three occasions.[2] In contrast to hypertension in adults, which is usually primary, hypertension in children is commonly due to secondary causes such as renal disease, cardiovascular disease, endocrine disorders and medications.[1]

Little data is available on the use of antihypertensive medications in children due to ethical concerns and strict testing requirements for the pediatric population.[1] With continued research and clinical experience, clinicians will have more evidence to guide decisions and select the most appropriate and efficacious medication. Practitioner familiarity with the pediatric population and available treatments for hypertensive emergencies will optimize patient outcomes. This review will present the possible medication options for the treatment of hypertensive emergencies in the pediatric population, with a focus on the dose, route of administration and other characteristics specific to each drug. Furthermore, roles for pharmacists in the prevention and treatment of these severe hypertensive episodes in pediatric patients will be discussed.

Severe Hypertension

Severe hypertension in children is defined as a blood pressure above the 99th percentile.[3] Hypertensive emergency can be identified by the presence of acute end-organ dysfunction. Clinical presentation of end-organ damage involve the central nervous system, eyes, heart, and kidneys and may manifest as seizures, retinopathy, cardiomegaly, congestive heart failure, tachypnea, and/or lethargy, among other presentations.[4] The type of acute end-organ damage determines the type of therapy used to treat these patients.

Pharmacotherapy for Hypertensive Emergencies

Hypertensive emergencies require immediate treatment. Several factors dictate which treatment option will be utilized, including the severity of the patient's clinical condition, type of end-organ damage, presumed cause, cardiac output, total peripheral resistance, and physician familiarity with the medications.[5] Hypertensive emergency is typically treated using intravenous (IV) medications to closely control reductions in blood pressure. The goal of treatment is to decrease blood pressure by up to 25 percent over the first six to eight hours, followed by a gradual reduction over the next 48 hours.[5,7] Treatment of hypertensive emergencies requires a controlled decrease in blood pressure to avoid severe hypotension, which may result in ischemia and necrosis due to changes in tissue autoregulation.[5]

Sodium nitroprusside

Sodium nitroprusside is an arteriolar and venous vasodilator with an instantaneous onset of action.[5] This advantage is somewhat offset by its 10-minute preparation time. The vial must be reconstituted with 5 percent dextrose in water or sterile water and then further diluted for continuous infusion via a volumetric infusion pump to allow for tightly controlled administration.[6] Additionally, the bottle, burette and syringe pump must be covered with an opaque protective covering to prevent degradation by light; amber plastic coverings are insufficient. Sodium nitroprusside decreases both cardiac preload and afterload with no chronotropic or inotropic effects.[7] It may be used when short-term reduction of cardiac preload and/or afterload is desired.[8] Cyanide toxicity is a concern with nitroprusside, and, according to manufacturer recommendations, failure to obtain the desired blood pressure control after maximum rate infusion (8-10 mcg/kg/min) for 10 minutes should result in termination of the infusion to avoid toxic cyanide levels.[6] Patients with hepatic or kidney dysfunction are more prone to accumulation of thiocyanate, and anuric patients should receive no more than 1 mcg/kg/min to avoid toxicity. Signs of cyanide toxicity may not appear until an hour after toxic levels have been reached. Administration of thiosulfate and methylene blue have been postulated as treatments for cyanide toxicity, but these should be used with caution as their routine use is not recommended. Nitroprusside may increase intracranial pressure and should not be used to treat compensatory hypertension due to aortic coarctation or arteriovenous shunting in patients with known inadequate cerebral circulation, or high-output heart failure.[6,7]

Nitroglycerin

Nitroglycerin is a potent vasodilator that reduces blood pressure by predominately decreasing preload and modestly reducing afterload.[9,10] It is mainly used as an adjunct in patients with hypertensive emergencies associated with acute coronary syndromes or acute pulmonary syndromes.[11] Its use is contraindicated in pericardial tamponade, restrictive cardiomyopathy and constrictive pericarditis.[6] The onset of action is

one to five minutes with a duration of action of five to 10 minutes after the infusion is discontinued.[9] Despite its favorable onset and duration, nitroglycerin is not considered a first-line treatment because of its potential to cause tachycardia and precipitous hypotension even in very small doses.[6,9] Methemoglobinemia has been observed in adults when doses greater than 7 mcg/kg/min were used; tachyphylaxis also has been seen in adults and can often be reversed by an eight-hour nitrate-free interval.[6] The infusion should be administered from a glass bottle using a non-polyvinyl chloride (PVC) set to prevent drug adsorption to the tubing. If a PVC set must be used, higher than expected doses may be required due to loss of drug in the tubing.[6]

Labetalol

Labetalol is a selective α_1 and non-selective β-blocker. It has an onset of action within two to five minutes and can be administered as an intermittent or continuous infusion.[5,9] Because labetalol is not cardioselective, it reduces blood pressure by producing both a modest reduction in heart rate and a decreased systemic resistance through vasodilation.[7] It may be a safe choice in patients with cerebrovascular disease or increased intracranial pressure because it does not further increase cerebral blood flow or intracranial pressure.[4] Labetalol is contraindicated in asthma, chronic lung disease, heart block, cardiogenic shock and heart failure. Dose adjustments are not required in patients with severe renal or hepatic dysfunction.[5] Like other β-blockers, labetalol may mask symptoms of hypoglycemia such as tachycardia.[7] If using labetalol in a patient suspected of pheochromocytoma or stimulant intoxication, specific assay methods such as high-performance liquid chromatography with solid-phase extraction should be used to avoid false-positive urine catecholamine tests. Additionally, labetalol may produce false positives if using the Toxi-Lab A or Emit-d.a.u. amphetamine assays.[6]

Esmolol

In contrast to the non-selective β-blocker labetalol, esmolol is a β_1 selective receptor antagonist that has an onset of action within seconds.[4,12] A significant advantage of esmolol is its short duration of action, approximately 10 to 20 minutes, and its extremely short half-life, which allows it to be easily titrated. Esmolol reduces blood pressure by decreasing cardiac output.[13] It is thus contraindicated in sinus bradycardia, in a greater than first-degree heart block unless a functional pacemaker is in place, cardiogenic shock and overt heart failure.[6] Esmolol is safer than labetalol in patients with asthma and obstructive lung disease but should still be avoided; if necessary, the smallest dose possible should be utilized.[7] Like labetalol, esmolol does not increase cerebral pressure or blood flow.[13] It does not require dose adjustments in renal or hepatic disease, although the half-life of the active metabolite may be increased tenfold in organ dysfunction.[6,7] Esmolol is more likely to cause thrombophlebitis and irritation when infused at concentrations greater than 10 mg/ml, and it may interfere with glucose and cholesterol tests.[6]

Hydralazine

Hydralazine is an arteriolar vasodilator with an onset of action of 30 minutes.[5] The duration is fairly unpredictable and may range from four to 12 hours.[7] Hydralazine is not as potent as sodium nitroprusside and may cause reflex tachycardia requiring administration of a β-blocker.[5] If a β-blocker and hydralazine are used simultaneously, the dose requirements of hydralazine are reduced.[6] This drug can produce renin-mediated sodium and fluid retention, which may necessitate the use of diuretics.[6,7] A unique feature of hydralazine is that it may be given intramuscularly to a patient who does not have an intravenous line established but requires immediate treatment.[7] It also can be given by IV push. Hydralazine should be used with caution in patients who have suffered a cerebrovascular accident.[6] It is contraindicated in patients with coronary artery disease and mitral valvular rheumatic heart disease. Especially in slow acetylators, hydralazine has the rare potential to induce systemic lupus erythematosus and related syndromes such as glomerulonephritis; if these develop, therapy with the agent should be re-evaluated. Hydralazine does require dose adjustments for patients in renal failure and further adjustments may be made if acetylator status is known. It should never be diluted in sugar-containing solutions due to the formation of toxic hydrazones. Peripheral neuritis may develop and may be treated with pyridoxine.

Nifedipine

Nifedipine is a calcium channel blocker administered sublingually and has an onset of action within 15-30 minutes.[5,11] This drug has the potential to produce a precipitous drop in blood pressure, which has made its use controversial. It is considered safer in children than it is in adults, and using a dose below 0.25 mg/kg may help minimize the risk of hypotension.[13,14]

Nicardipine

Nicardipine is also a calcium channel blocker.[5] It has a favorable onset of action within minutes.[4,9] Nicardipine is an excellent medication for emergencies because it can be easily prepared and titrated, although it can only be given by continuous IV infusion.[5,6] It has been shown to be safe and effective in treating hypertensive emergencies in children and to be as effective as nitroprusside in adults without the risk of cyanide toxicity.[13] Nicardipine is quite selective for the peripheral vasculature. It produces vasodilation of cerebral and coronary vessels with little effect on the heart, although there is a small chance of reduced heart rate. Thus, this medication is contraindicated in patients with advanced aortic stenosis and the manufacturer recommends caution in patients with heart failure and left ventricular dysfunction, especially when concomitant β-blockers are administered.[6] A few reports of reflex tachycardia do exist.[7] Propranolol has been used to treat reflex tachycardia, but caution must be used to avoid hypotension.[6] In contrast to labetalol, nicardipine may be safely used in patients with bronchospastic diseases.[7] There have been reports of thrombophlebitis when given through peripheral IV; if administering by this route, rotating sites every 12 hours may reduce the risk of thrombophlebitis.[13] The normal concentration for administration by peripheral IV is 0.1 mg/ml; higher concentrations up to 3.6 mg/ml have been given safely via central lines.[6] Another disadvantage of nicardipine is that it may cause an increase in intracranial and intraocular pressure; its use is thus discouraged in patients with suspected intracranial masses or space-occupying lesions.[7,13] Although no specific dosing recommendations exist for use in renal or hepatic failure, conservative doses are recommended.[6]

Fenoldopam

Fenoldopam is a dopamine D_1 receptor agonist that causes vasodilation of coronary, cerebral, renal and splanchnic vasculature, leading to a dose-dependent decrease in blood pressure.[7,9] It also has been associ-

ated with short-term increases in urine output and creatinine clearance.[13] There are some reports of reflex tachycardia with large doses; in some pediatric patients, the tachycardia lasted four hours or more.[6] Doses greater than 1.2 mcg/kg/min intravenously have been associated with greater tachycardia without greater hypotensive effect.[7] No dose adjustments are required in renal or hepatic dysfunction. Notably, the dosage range for fenoldopam in children is significantly higher than the adult range, suggesting that fenoldopam may have lower efficacy in children than in adults. There are reports of hypokalemia and increased intracranial and intraocular pressure in adults.[6,7,13] When used for longer than 48 hours, tolerance may develop.[13] In adults, fenoldopam was shown to have similar efficacy and safety as nitroprusside in the treatment of hypertensive crisis but was much more costly; however, fenoldopam has no risk of cyanide toxicity. Concomitant use with β-blockers should be avoided to reduce the chance of severe hypotension as β-blockers inhibit the sympathetic reflex response to fenoldopam.[6]

Enalaprilat

Enalaprilat is an angiotensin converting enzyme inhibitor (ACE-I) that is useful in renin-dependent hypertension.[7] Enalaprilat may be given by either IV push or intermittent infusion but is not appropriate for use in a continuous infusion.[6] Its use is contraindicated in patients with a history of angioedema due to ACE-Is and hereditary or idiopathic angioedema because anaphylactoid reactions requiring immediate airway management have occurred.[6] Enalaprilat can be difficult to titrate due to its slow, hour-long onset and extended duration.[15] This medication also has the potential to cause renal failure, especially in the neonate in whom the drug is eliminated more slowly and has an extended duration of action.[6,7] It requires dose adjustment in renal failure.[6] Clinicians should be aware that the formulation contains benzyl alcohol, which has been associated with the Gasping Syndrome (metabolic acidosis progressing to respiratory distress and gasping respirations). Transient hyperkalemia has been observed in adults.

Role of Pharmacists

Pharmacists can play an active role in both preventing and treating hypertensive emergencies in pediatrics. In the community setting, they can play a proactive role by counseling the parents of pediatric patients, especially those with hypertension, on the importance of adherence, possible drug interactions (especially with monoamine oxidase inhibitors) and other concerns with the different classes of drugs. For pediatric patients diagnosed with hypertension, the pharmacist can monitor blood pressure by performing blood pressure checks between physician appointments. The pharmacist should ensure the use of the proper cuff size to prevent errors in measurement. Pharmacists can also educate parents on poison prevention safety to avoid accidental ingestion of drugs that may cause hypertensive emergencies.

Health-system pharmacists can develop guidelines to facilitate optimal treatment of pediatric patients with hypertensive emergencies. They can take complete medication histories to identify drug-related causes of hypertensive emergencies and assist in the selection and modification of therapy. They should also ensure that proper weights, heights, and renal and hepatic function have been documented to ensure accurate dosing.[7]

Conclusion

Pediatric hypertension has become more prevalent within the last decade. There are many possible causes of hypertension in this population. Patients can present with hypertensive urgency or emergency, which are differentiated by the presence of acute end-organ dysfunction and are treated accordingly. There are many different agents used in the treatment of hypertensive emergencies with the majority of them being administered parenterally with a rapid onset of action and easy titration to prevent hypotension. The treatment of hypertensive emergencies in pediatric populations has not been extensively studied due to strict testing guidelines. This leaves a great deal of room for advancements in therapy options for pediatric hypertensive emergencies, as current treatment is generally guided by experience and expert consensus. Optimal treatment of children with hypertensive emergencies may be impaired by unfamiliarity with available agents and paucity of evidence on which to base clinical decisions. Pharmacists and other clinicians must be cognizant of the special issues involved in treating pediatric patients and familiar with best practices to ensure the safe and appropriate treatment of pediatric patients with severe hypertension.

Table 1: Common Medications for the Treatment of Pediatric Hypertensive Emergencies

Generic Drug Name	Mechanism of Action	Dose	Route	Onset of Action	Duration of Action
Sodium Nitroprusside[5,6]	Vasodilator	0.25-10 mcg/kg/min	Continuous IV infusion	Within seconds	1-10 min
Nitroglycerin[6,9]	Vasodilator	0.25-10 mcg/kg/min	Continuous IV infusion	1-5 min	5-10 min
Labetalol[5,6,9]	α_1 and non-selective β-adrenergic blocker	0.25-1 mg/kg/hr (bolus) or 0.25-3 mg/kg/hr (continuous)	IV bolus or continuous IV infusion	2-5 min	2-4 hr
Esmolol[4,9,12]	β_1 selective β-blocker	500-600 mcg/kg loading dose, then 100-500 mcg/kg/min	Continuous IV infusion	Immediate	10-30 min
Hydralazine[5,6,7]	Vasodilator	0.2-0.6 mg/kg every 4 hr	IV	5-30 min	2-6 hr
Nifedipine[5,11,14]	Calcium channel blocker	0.2-0.5 mg/kg/dose	Peroral	5-15 min	8 hr
Nicardipine[4,6,9]	Calcium channel blocker	1-5 mcg/kg/min	Continuous IV infusion	Within minutes	4-6 hr
Fenoldopam[6,7,9]	D1 receptor agonist	0.2-0.8 mcg/kg/min	Continuous IV infusion	5 min	30-60 min
Enalaprilat[6,7,15]	Angiotensin converting enzyme inhibitor	5-10 mcg/kg/dose	IV push or intermittent IV infusion	1 hr	24 hr

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