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FDA Approved Pediatric Antihypertensive Agents Ashish Doshi

When choosing a long-term antihypertensive agent in a patient, several factors should be considered: Indications or contraindications with respect to co-morbid conditions, side effect profile, availability of liquid preparations, dosing interval, and medication cost and generic availability. Knowledge of which agents are FDA-approved and have undergone trials in children aids in safe prescribing, but should not prevent one from prescribing an agent not FDA-approved in children. This chapter will review major medication classes, mechanism of action, representative agents including those approved in children, common or important side effects, contraindications, and beneficial populations.

Diuretics

In adults, diuretics have been proven to be as effective as ACE inhibitors or calcium-channel blockers in preventing fatal coronary heart disease or nonfatal myocardial infarction, and perhaps more effective in decreasing blood pressure.¹ Thiazide diuretics are one of four classes of antihypertensives recommended as first-line therapy for hypertension in adults, the other classes being ACE inhibitors, ARBs, and calcium channel blockers.² Thiazide diuretics acutely decrease blood pressure by blocking the sodium-chloride symporter in the distal tubule, thus preventing salt and water reabsorption and promoting natriuresis and diuresis. Loop diuretics interfere with the sodium-potassium-chloride cotransporter in the thick ascending limb of the loop of Henle, thus causing natriuresis and diuresis. The long-term antihypertensive mechanism of diuretics is less well-understood. Of the diuretics, only hydrochlorothiazide is FDA-approved in children.³ Other diuretics with pediatric experience include chlorthalidone and furosemide. Furosemide is FDA-approved for the treatment of edema but can be used as add-on therapy for hypertension. Chlorthalidone can precipitate azotemia and therefore should be used with caution in patients with renal disease. Spironolactone, triamterene, and amiloride are potassium-sparing diuretics with pediatric experience. For all diuretics, electrolytes should be

monitored periodically, particularly for potassium-sparing diuretics, which can cause hyperkalemia, especially when used in conjunction with an ACE inhibitor or ARB.

ACE inhibitors and ARBs

ACE inhibitors are the most-commonly prescribed agents for pediatric hypertension.⁴ ACE inhibitors are direct antagonists of angiotensin-converting enzyme, thus reducing the conversion of angiotensin I to angiotensin II. Angiotensin II is a potent vasoconstrictor with the greatest vasoconstrictive action on the efferent arteriole versus the afferent arteriole. Additionally, it stimulates secretion of aldosterone from the zona glomerulosa cells of the adrenal glands and induces release of vasopressin from the pituitary; ACE inhibitors therefore decrease blood pressure through a number of mechanisms. ACE inhibitors can be renoprotective in patients with diabetes.⁵ Benazepril, enalapril, fosinopril, and lisinopril are all FDA-approved in children over 6 years of age with creatinine clearance over 30 mL/min per 1.73 m².³ Without the action of angiotensin II the afferent arteriole of the glomerulus becomes more constricted than the efferent arteriole (or one could say the efferent arteriole becomes more dilated as there is no angiotensin II to cause efferent arteriole vasoconstriction). This causes decreased glomerular pressure and in low-volume states such as dehydration or ineffective circulating volume (cardio-renal/hepato-renal syndromes) results in acute decreased glomerular filtration. Therefore, adequate intravascular volume must be maintained during ACE inhibitor therapy.^{6,7} Captopril and quinapril also have pediatric experience. Electrolytes and renal function should be monitored periodically as hyperkalemia and azotemia are potential risks. Cough and angioedema are other fairly common side effects: cough reported in up to 12% of patients; angioedema -1 case per 1000 (0.1%) with captopril and enalapril, 1 case per 200 (0.5%) with lisinopril.⁸ Females of childbearing age must have reliable contraception, as ACE inhibitors are teratogenic.

Angiotensin receptor blockers are similar to ACE inhibitors in their indications. They block the angiotensin II receptor, preventing angiotensin II from causing vasoconstriction or

release of vasopressin from the pituitary. The main reason for using an ARB over an ACE inhibitor is due to the decreased side effect profile (less incidence of cough and angioedema, though hyperkalemia, azotemia, and teratogenicity remain risks). In theory, because the reduction in the amount of circulating angiotensin II due to ACE inhibitors is dose-dependent, combination therapy with an ACE inhibitor and an ARB may be more beneficial than using a single agent alone. However, combination therapy has not been found to provide greater benefit and at least in the diabetic population has been shown to increase the risk of hyperkalemia and acute kidney injury.⁹ Irbesartan, losartan, and candesartan are all FDA-approved ARBs in children over 6 years of age with creatinine clearance over 30 mL/min per 1.73 m².³

Beta blockers

Beta blockers antagonize the beta adrenergic receptor. Cardioselective beta blockers inhibit beta-1 receptors in the heart and kidney, decreasing inotropy and chronotropy as well as renin release. Non-cardioselective beta blockers inhibit both beta-1 receptors as well as beta-2 receptors. Propranolol is the only FDA-approved beta-blocker in children.³ As a non-cardioselective agent, its use is contraindicated in patients with asthma. Cardioselective agents with pediatric experience include metoprolol and atenolol. Labetalol is a combined alpha- and non-cardioselective beta-blocker and as such should also not be used in patients with asthma. The additional peripheral alpha-1 blockade relaxes vascular smooth muscle, aiding in the antihypertensive effect. For all of these medications, bradycardia is the limiting factor in titrating up the dose. In addition, the blunting of appropriate tachycardia may reduce athletic performance. Beta-blockers should not be used in insulin-dependent diabetics as beta-2 activation stimulates hepatic glycogenolysis, helping to keep blood sugar levels stable.

Calcium channel blockers

Amlodipine is the only FDA-approved calcium channel blocker in children.³ Felodipine, isradipine, and extended-release nifedipine also have pediatric experience. Calcium channel

blockers inhibit L-type calcium channels in the heart and in vascular smooth muscle. They reduce blood pressure by decreasing myocardial chronotropy and inotropy as well as causing arterial and arteriolar dilation. In all calcium-channel blockers, reflex tachycardia can result from peripheral vasodilation.

Central alpha agonists

Clonidine is FDA-approved in children over 12 years.³ It acts as an agonist on central alpha-2 receptors in the vasomotor center of the brainstem, thus decreasing norepinephrine release and decreasing vascular tone. In addition to the oral preparation, a transdermal patch preparation is available. Patients should be monitored for anti-cholinergic side effects such as dry mouth or sedation. Suddenly discontinuing the agent can result in severe rebound hypertension.

Peripheral alpha antagonists

Doxazosin, prazosin, and terazosin have all been studied in children, though none of them are FDA-approved. These agents inhibit binding of norepinephrine to alpha-1 adrenergic receptors on vascular smooth muscle, thus causing vasodilation. These agents are infrequently used, mainly due to available alternative agents with more pediatric experience. In adults, the large ALLHAT study showed that doxazosin was less effective than diuretics at reducing blood pressure, and the doxazosin study arm was stopped due to an increased rate of cardiovascular disease and congestive heart failure.¹ Peripheral alpha antagonists can sometimes cause hypotension or syncope when starting therapy.

Direct vasodilators

Hydralazine and minoxidil are both FDA-approved in children.³ Hydralazine activates potassium channels in vascular smooth muscle cells, thus hyperpolarizing them and preventing the increase in intracellular calcium necessary for smooth muscle contraction.¹⁰ Because of the direct vasodilation, reflex tachycardia and fluid retention (from increased venous capacitance) can be seen. Minoxidil's mechanism of action is not well-understood but is thought to largely be

due to activation of potassium channels¹⁰ with a mechanism similar to that of hydralazine.

Minoxidil is well-known as a topical preparation to treat androgenetic alopecia,¹¹ so one of the side effects of oral minoxidil is hypertrichosis. Hypertrichosis usually resolves 1-6 months after stopping therapy.

Medication * = FDA approved in pediatric population.	Dose	Comments
Hydrochlorothiazide*	<6 mos: 2-4mg/kg/day >6 mos 1-2 mg/kg/day; usually twice daily; Max dosing >6mos-2 years= 37.5mg day >2 years= 100mg/day	
Lisinopril*	0.7mg/kg/day; usually once daily; Max dosing 0.6mg/kg/day up to 40mg/day	
Enalapril*	0.8mg/kg/day; usually twice daily; Max dosing 0.6mg/kg/day up to 40mg/day	
Candesartan*	<6 years: 0.2 mg/kg/day >6 years <50kg: 4-8 mg daily >6 years >50kg: 8-16 mg daily usually once daily; Max dosing 32 mg/day	
Losartan*	0.7 mg/kg/day; usually once daily ; Max dosing 1.4 mg/kg/day up to 100 mg/day	
Valsartan*	1.3 mg/kg/day; usually once daily; Max dosing 2.7 mg/kg/day up to 160mg/day	Exposure to valsartan in suspension is 1.6 times greater than the tablet form.
Propranolol*	1-2 mg/kg/day; usually twice daily; Max dosing 8 mg/kg/day up to 640 mg/day	
Labetalol	1-3 mg/kg/day; usually twice daily; Max dosing 10-40 mg/kg/day up to 1200 mg/day	

Medication	Dose	Comments
* = FDA approved in pediatric population.		
Amlodipine*	2.5 -10 mg/day; once daily dosing; Max dosing 10mg	
Nifedipine	0.1-0.2 mg/kg/dose; usually given q. 4 hours; Max dosing 0.5 mg/kg/dose	Can cause abrupt blood pressure reduction to hypotensive levels.
Clonidine*	0.05mg once daily; usually give TID; Max dosing 0.6 mg/day	
Transdermal Clonidine*	Applied every 7 days	
Doxazosin	1 mg once daily; usually give once daily; Max dosing 4mg/day	
Hydralazine*	0.75mg/kg/day; usually in 4 divide doses; Max dosing 7.5mg/kg or 200mg daily	
Minoxidil*	0.2mg/kg/day; usually once daily; Max dosing 50mg/day	

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