Review

Efficacy and Safety of Angiotensin Receptor Blockers in Pediatric Patients (Aged 6 to 18) with Hypertension: A Systematic Review

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Angiotensin receptor blockers (ARBs) are commonly prescribed in pediatric hypertension because of the fundamental role of the renin-angiotensin-aldosterone system in the pathogenesis of hypertension. We, therefore, aimed to systematically review articles that investigated efficacy and safety of ARB agents in the pediatric population aged over six years. To do so, the databases of Web of Science, PubMed/MEDLINE, and Scopus were searched to conduct a systematic review by using the following keywords: ("angiotensin receptor blocker" OR "valsartan" OR "losartan") AND ("pediatric" OR "children" OR "child") AND ("high blood pressure" OR "hypertension"). Finally, 12 studies were included in our review, and we found that almost all of them supported the effectiveness and tolerability of different ARB agents. Candesartan cilexetil lowered blood pressure (BP), with a 9 mmHg decline in both systolic and diastolic BP, and proteinuria after four months of treatment. Valsartan and Losartan similarly were shown to be effective in lowering BP in a dose-dependent manner. Headache, dizziness, upper respiratory infection, and cough were the most reported side effects. However, almost all reviewed studies indicated that the safety profile was satisfactory. In conclusion, ARBs are beneficial and well-tolerated antihypertensive medications.

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INTRODUCTION

Pre-hypertension and hypertension in the pediatric population are prevalent in about 10 and 4 percent of children, respectively. This is[1] primarily due to the effects of increased childhood obesity.[2,3] End organ damage is recognizable in hypertensive children, who are at risk of developing hypertension as adults.[4-9] Since many children and adolescents who require antihypertensive medications have some degree of kidney impairment. Agents that block the renin–angiotensin system, primarily the angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin II receptor blockers (ARBs), are the most prescribed drugs,[10] and are recommended as the first-line treatment for diabetes with microalbuminuria or proteinuria.[11]

ARBs are believed to have an advantage over ACEIs, as ACEIs do not block tissue and serum converting enzyme angiotensin I to II, thereby avoiding the renin-angiotensin-aldosterone system blockade.[12,13] The limited data on efficacy and side effects of antihypertensive medications in children have impeded the accurate treatment of high blood pressure in this age group. ARBs account

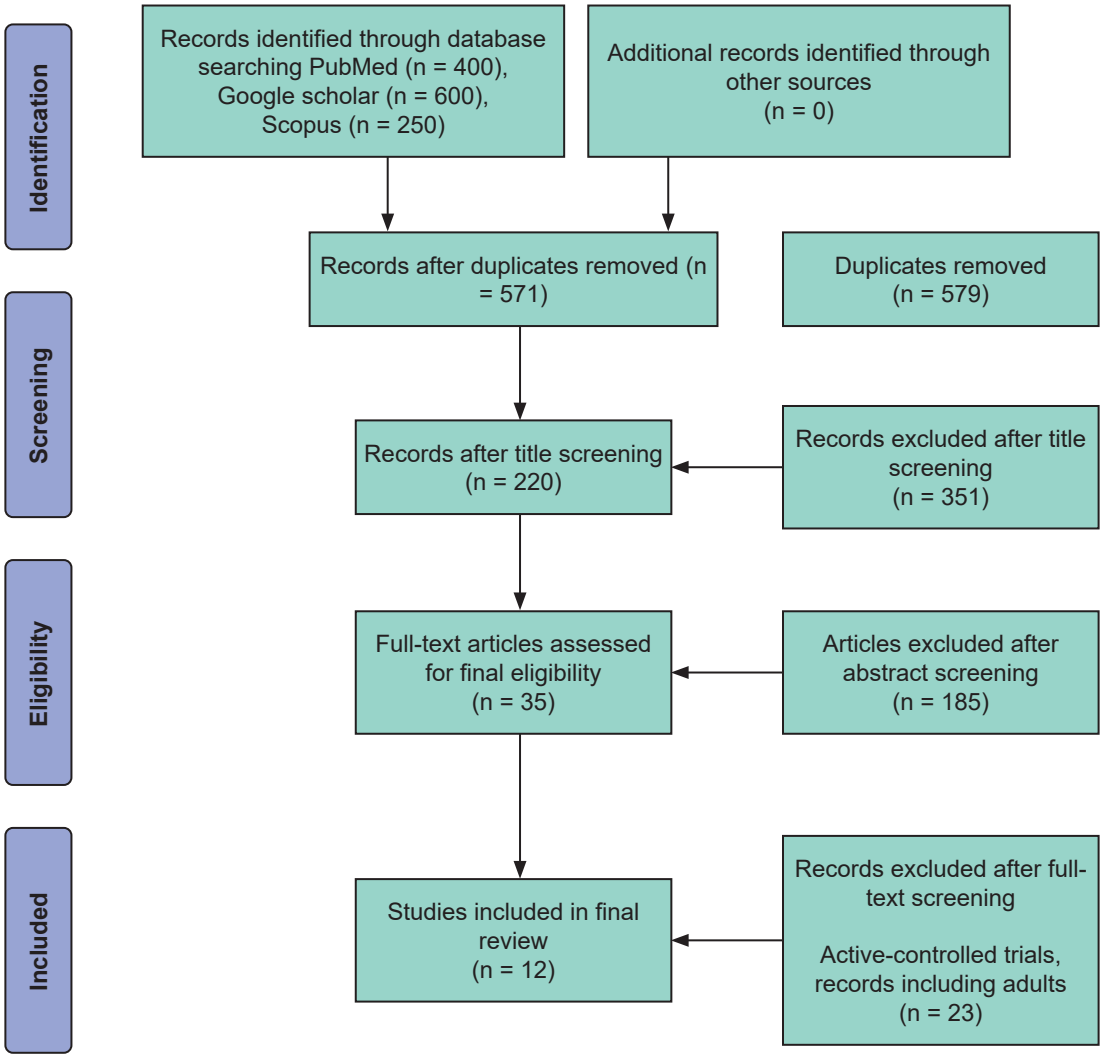
for 15% of the estimated prescribed medications for hypertensive children between 6 to 17 years old,[14] however, studies on the benefits and side effects of these medications in hypertensive children have some scattered data,[15-17] and ARBs have not systematically and comprehensively been investigated till lately.

The present study aimed to systematically review original articles that investigated efficacy and safety of ARB agents in the pediatric population aged over six years.

MATERIALS AND METHODS

Literature Search Strategy and Study Selection

While conducting this systematic review, we followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement guidance.[18] The databases of Web of Science, PubMed/MEDLINE, and Scopus were searched systematically up to April 2022. Direct for the following keywords or MeSh-terms: ("angiotensin receptor blocker" or "valsartan" OR "losartan") AND ("pediatric" OR "children" OR "child") AND ("high blood pressure" OR "hypertension") was the search strategy. We also searched through the references of the articles we found to see if there were any other studies potentially applicable. We did not include grey literature because there are several characteristics that make it difficult to search systematically, and no gold standard for a comprehensive systematic search of grey literature is recommended. We studied English articles, and there were no time restrictions or other filters in place. The following



Search Strategy Flow Chart, Demonstrating the Systematic Search and Excluded Reports at Each Step

PICOTD methodology was used: P (Problem): hypertension; I (Intervention): angiotensin receptor blocker treatment; C (Comparison): intervention and control, or before and after the treatment; O (Outcomes): efficacy and safety; T (Timing): ≥ three weeks follow-up; D (Design): clinical trial observational original studies. Figure depicts the search strategy, the studies discarded and included at each step based on the criteria.

Data Extraction

This systematic review enrolled clinical studies that evaluated the efficacy and safety of angiotensin receptor blockers on children between 6 to 18 years old, in a single- or double-group clinical trial, observational, or cross-sectional setting. Two reviewers reviewed the study titles and abstracts independently to choose the relevant ones. Duplicate reports were removed, and applicable articles were imported into the citation manager software (Endnote V9). Irrelevant studies, as well as laboratory experiments, ARBs directly versus active comparator, case reports, case series, papers including adult individuals, book chapters, and letters to editors, were among the excluded items.

Clinical trials were assessed using the JADAD scale (Jadad scoring or the Oxford quality scoring system, is a procedure to assess the methodological quality of a clinical trial by objective

criteria). Studies were scored according to the randomization, masking, and eligibility of all patients, and withdrawals. The total score was between 0 and 5. Studies scored ≥ 3 were considered as good quality. Observational studies were assessed by using the Newcastle Ottawa scales (NOS). Articles with at least five stars were considered as good quality. Two reviewers collected data from full texts of included articles by using a customized Excel sheet. The data retrieved included author, year, country, study type, sample size, participants age, participants condition, ARB agent and dosage, exposure (medicine and dosage), follow-up duration, results on efficacy and safety, and conclusion.

RESULTS

Literature Search

Twelve studies were finalized for review. The mostly investigated ARB agents, were Candesartan Cilexetil (n = 3), Valsartan (n = 3), and Losartan (n = 2). Other agents were Olmesartan, Medoxomil, Telmisartan, and Azilsartan, each having one article. Most of the articles were randomized and open-label trials. The information of studies included are presented in Table 1.

Systematic Review of Efficacy and Safety of ARBs

Efficacy. While conducting a randomized, double blind, placebo-controlled study, Trachtman *et al.* reported that systolic blood pressure decreased 8.6 to 11.2 mmHg, after four weeks of treatment with Candesartan Cilexetil (selective inhibitor of the angiotensin II, type 1 receptor).[19] Continuing the open-label trial, a 53% response rate was achieved after one year.[19] Another study on this new agent showed a mean of 9 mmHg decrease in both systolic and diastolic blood pressure after 4 months of treatment.[20] A pilot single-group trial showed 7.4 and 5.9% decline in blood pressure after two weeks of treatment with Candesartan Cilexetil.[21]

Losartan also led to a sustained reduction in diastolic and mean arterial pressure in a long-term follow-up study, after more than two years, with dizziness as the most common complication reported in 11 percent of patients.[22] During a dose-response study, Olmesartan Medoxomil lowered blood pressure efficiently (a significant difference of 3.6 mm Hg between Olmesartan and placebo (P = .0093)), and with an acceptable safety profile.[23] Shahinfar *et al.* demonstrated a dose-dependent response with Losartan 12.5 to 100 mg/d in hypertensive children above six years old.[24] A placebo-controlled trial in the pediatric population also reported that Telmisartan 1 to 2 mg/kg/d could be an effective medicine to treat hypertension.[25] A long-term open-label prospective study on Azilsartan resulted in acceptable efficacy and safety with a daily dose of 2.5 to 5 mg/kg.[26]

Valsartan was consistently the beneficial blood pressure lowering agent in Lou-Meda *et al.* open-label study with a mean of 14.9/10.6 mmHg decline in blood pressure after 78 weeks of treatment.[27] Re-randomization revealed that non-obese patients receiving placebo but not Valsartan experienced an increase in blood pressure, but obese patients' blood pressure increased in both treated groups.[28] In this trial, sitting BP decreased about 7.4 to 13.9 mmHg, depending on the treated dosage from 10

Table 1. Characteristics of the Reviewed Articles

N	Year	Author	Study type	Age Range (year)	Sample Size	Condition	ARB Agent	Dosage	Follow-up (weeks)	Quality Score
1	2008	Howard Trachtman et al.	Randomized, double-blind, placebo-controlled	6 to 17	240	Primary Hypertension	Candesartan Cilexetil	W < 50 kg: 2, 8, and 16 mg/d W ≥ 50 kg: 4, 16, and 32 mg/d	4	5
			Open-label trial	6 to 17	233			Beginning: 4 or 8 mg/d, adjust doses between 2 and 32 mg	52	5
2	2006	Giacomo D. Simonetti et al.	Single-group trial	0.5 to 16	17	Glomerular disease (n = 11), Polycystic kidney disease (n = 3), Renal transplant (n = 2), and Essential hypertension (n = 1)	Candesartan Cilexetil	0.35 (0.22 to 0.47) mg/kg	16	5
3	2004	Demetrius Ellis et al.	Observational	12.85	45	Chronic renal parenchymal disorders	Losartan	Beginning: 25 mg/m2/d, or 0.8 mg/kg/d	120	5
4	2010	Lydie Hazan et al.	Dose-Response clinical trial	6 to 16	302	Hypertension	Olmesartan Medoxomil	20-35 kg: 2.5 or 5 mg/d ≥ 35 kg: 20 or 40 mg/d	5	5
5	2011	Thomas Wells et al.	Double-blind, randomized, study	6 to 16	261	Hypertension	Valsartan	< 35 kg: 10 mg (low dose), 40 mg (medium dose), or 80 mg (high dose) ≥ 35 kg: 20 mg (low dose), 80 mg (medium dose), or 160 mg (high dose)	4	4
			Open-label trial		_			Beginning; 40 mg/d	52	5
6	2008	Amy M Franks et al.	Pilot study	14.2	11	Hypertension	Candesartan Cilexetil	0.13 mg/kg, Range 2 to 16 mg	2	5
7	2005	Shahnaz Shahinfar et al.	Randomized, dose-response study	6 to 16	175	Hypertension	Losartan	low, 2.5/5.0 mg; middle, 25/50 mg; or high, 50/100 mg	5	5
8	2010	Thomas G. Wells et al.	Randomized clinical trial	6 to 18	77	Hypertension	Telmisartan	1 mg/kg/d or 2 mg/kg/d	4	5
9	2021	Shuichi Ito et al.	Open-label, prospective study	6 to 15	27	Hypertension	Azilsartan	W < 50 kg: 2.5 mg/d (titrated up to a maximum of 20) W ≥ 50 kg: 5mg/d (titrated up to a maximum of 40)	52	5
10	2019	Randall Lou-Meda et al	Open-label, prospective study	6 to 17	117	Hypertension	Valsartan	Beginning: 40, 80 or 160 mg (after 1 week, the dose was force titrated to 80, 160 or 320 mg, respectively.)	72	5
11	2001	Abdullah Sakarcan et al.	Open-label	1 to 16	23	Hypertension	Irbesartan	2 mg/kg/d; maximum 150 mg/d	2 to 4	5
12	2011	Meyers et al.	Randomized, double-blind, placebo-controlled	6 to 16	261	Hypertension	Valsartan	10 to 160 mg/d	4	5
			Open-label trial		117			Beginning; 40 mg/d	52	5

Abbreviations: N, number; W, weight; d, day.

to 160 mg, once daily.[28] It has also been shown that Irbesartan 2mg/kg/d decreased blood pressure effectively (16/10 mmHg decline) when applied for 2 to 4 weeks in hypertensive children.[29]

Safety. In general, ARBs were reported to be well tolerated in most studies. All reviewed articles, except one, reported headache as the most commonly reported adverse effect (AE) among patients. Dizziness was the second widely stated AE, in eight articles. Upper respiratory infection, pharyngitis, pharyngeal pain, sore throat, and toothache symptoms were reported in six studies. Cough was one of their noted side effects in four trials.[19,25,27,28] Hypotension was safety profile results[19,22,24,25,28] in five articles. On the other hand, unexpected elevated blood pressure was reported in one study with Olmesartan which resulted in its discontinuation.[23] Other reported symptoms included arm fracture (probably due to falling as the result of orthostatic hypotension),[19] fatigue,[21,22] weakness,[25] syncope,[22,25,26] nausea,[21,22,28] diarrhea,[21,28] pyrexia,[25,27-29] and epistaxis.[22,28] Laboratory findings included worsening of kidney function (increased serum creatinine level) among patients with underlying disorders,[19,25-27] elevated serum potassium level, [20,22-24] decreased urine albumin to creatinine ratio,[20,27] increased alanine transaminase (ALT),[24] and decreased platelet count.[24] Regarding electrocardiography, one study reported QT prolongation with Irbesartan.[29] Lupus nephritis and pneumonia were among AEs in Lou-Monde *et al.* study, investigating Valsartan treatment for 72 weeks.[27] The efficacy and safety of medications are presented in Table 2.

Table 2. Efficacy and Safety Outcomes of the Reviewed articles

N	Year	Author	ARB agent	Efficacy	Safety (discontinued N and AEs)	Conclusion
1	2008	Howard Trachtman et al.	Candesartan Cilexetil	↓SBP: 8.6 to 11.2 mmHg ↓DBP: 4.8 to 8 mmHg	(3) Headache Upper respiratory infection Dizziness Cough Sore throat Hypotension Arm fracture Low WBC Progression of underlying Kidney disorder	For children aged 6 to 17, Candesartan Cilexetil (2 to 32 mg) given once a day is an efficient and well-tolerated anti- hypertensive medicine.
				Response rate: 53%	(5) Headache Upper respiratory infection Dizziness Cough Sore throat Hypotension Arm fracture Low WBC Progression of underlying Kidney disorder	
2	2006	Giacomo D. Simonetti et al.	Candesartan cilexetil	↓SBP: 9 (3 to 13) mmHg ↓DBP: 9 (3 to 18) mmHg	(0) ↑ Plasma K ↓ Alb/Cr (patients with overt proteinuria)	Candesartan lowers blood pressure and proteinuria in children and is well-tolerated in short treatment.
3	2004	Demetrius Ellis et al.	Losartan	↓SBP: 12 mmHg ↓DBP: 9 mmHg ↓MABP: 10 mmHg All three BP measures remained lower than at baseline at all visits	(5) Dizziness/lightheadedness (n = 7) Headache (n = 5) Fatigue/asthenia (n = 3) Syncope (n = 2) Blurred vision (n = 2) ↑ Serum Cr (n = 2) Hypotension (n = 1) Nausea/vomiting (n = 1) Hyperkalemia (n = 1) Epistaxis (n = 1)	Long term well tolerated and efficient.

Table 2. Continued

N	Year	Author	ARB agent	Efficacy	Safety (discontinued N and AEs)	Conclusion
4	2010	Lydie Hazan et al.	Olmesartan Medoxomil	Low dose: ↓7.8/5.5 mmHg High dose: ↓12.6/9.5 mmHg Significant dose response difference with placebo: 3.16 mmHg; P = .0029	(3) Hyperkalemia Headache Pharyngo-laryngeal pain Dizziness Toothache ↑ BP (n = 2) Hypoesthesia	In children with hypertension, Olmesartan Medoxomil was found to be both safe and effective.
5	2011	Thomas Wells et al.	Valsartan	Low dose: ↓7.9/4.6 mmHg; Medium dose: ↓9.6/5.8 mmHg; High dose: ↓11.5/7.4 mmHg [P < .001]	(4) Headache Dizziness Orthostatic hypotension Diabetes	Systolic and diastolic blood pressure were reduced dose-dependently.
				–	(7) Nasopharyngitis Pyrexia Cough Upper respiratory tract infection Headache Diabetes Acute gastroenteritis Hyperkalemia (transplant patient) ↑ Cr (transplant patient)	–
6	2008	Amy M Franks et al.	Candesartan Cilexetil	SBP: ↓7.4%, P = .03 DBP: ↓5.9%, P = .01	↓ Urine Cl Headache (n = 7) Dizziness (n = 5) Nausea (n = 4) Diarrhea (n = 4) Fatigue (n = 2)	In hypertensive children, Candesartan Cilexetil reduced blood pressure effectively and was well tolerated.
7	2005	Shahnaz Shahinfar et al.	Losartan	Low dose: ↓4.4/6 mmHg; Medium dose: ↓10/11.7 mmHg; High dose: ↓8.6/12.2 mmHg	(1) Headache (n = 5) Upper respiratory infection Hypotension (n = 1) ↑ ALT (n = 2) ↑ Cr (n = 1) ↑ Plasma K ↑ Platelet	Losartan lowered blood pressure in a dose-dependent manner.
8	2010	Thomas G. Wells et al.	Telmisartan	Low dose: SBP ↓9.7 mmHg High dose: SBP ↓14 mmHg	Dizziness Weakness Headache Near syncope (n = 1)	Telmisartan could be an effective treatment for hypertension in children.
9	2021	Shuichi Ito et al.	Azilsartan	SBP: ↓12.4 mmHg DBP: ↓13.9 mmHg	(2) Kidney transplant rejection, complications of transplanted kidney, and acute Kidney injury [AKI] (n = 1) Varicella (n = 1) ↑ Cr (n = 1) Dizziness Headache Postural dizziness Syncope Renal impairment	Azilsartan has the potential to be a promising treatment for pediatric hypertension with acceptable safety.

DISCUSSION

The present review study investigated the effectiveness and safety profile of the ARB medications among the pediatric population over six years old. In general, we noticed an agreement upon favorable efficacy and acceptable tolerability in different studies on various agents. Nearly the study population of all the reviewed studies fitted the epidemiologic characteristics of hypertension in this age group, and it was closely correlated

Table 2. Continued

N	Year	Author	ARB agent	Efficacy	Safety (discontinued N and AEs)	Conclusion
10	2019	Randall Lou-Meda et al.	Valsartan	SBP: ↓14.9 mmHg DBP: ↓10.6 mmHg	↓ Urine Alb/Cr (CKD patients) Mild AE (50.7%) Moderate AE (18.7%) ↓ Schwartz eGFR Lupus nephritis (n = 4) Pneumonia (n = 2) Cough Headache Pyrexia Nasopharyngitis Dizziness	Valsartan was well tolerated in the general population and in patients with underlying CKD, with an AE profile similar to that of angiotensin receptor blockers. Long-term efficacy was noted, as well as a positive effect on proteinuria.
11	2001	Abdullah Sakarcan et al.	Irbesartan	SBP: ↓16 mmHg DBP: ↓10 mmHg	Fever and vomiting (patient with sickle cell anemia) QT prolongation (n = 1) Headache (n = 2) Pharyngitis (n = 2)	Irbesartan was well tolerated and could be used as a possible treatment for children with hypertension.
12	2011	Meyers et al.	Valsartan	MSBP: ↓ 7.4 to 13.9 mmHg		In obese and non-obese hypertensive children, valsartan has similar antihypertensive effectiveness.
					Headache Fever Nasopharyngitis Cough Upper respiratory tract infection Diarrhea Vomiting Abdominal pain Influenza Sinusitis Nausea Nasal congestion Pharyngolaryngeal pain Dizziness Epistaxis Orthostatic hypotension ↑ Blood Cr	Good tolerability

Abbreviations: N, number; SBP, systolic blood pressure; DBP, diastolic blood pressure; MABP, mean arterial blood pressure; MSBP, mean sitting blood pressure; Cr, creatinine; K, potassium; GFR, glomerular filtration rate; ALT, alanine transaminase.

to weight and usually essential hypertension.[11,30]

Significant BP lowering has been observed across the dosage levels of Candesartan Cilexetil tested as compared with placebo.[19] However, the maximum doses seemed not to reduce blood pressure more significantly.[19] Similarly, Losartan revealed no significantly higher efficacy, when titrating the middle dose up to the high dose levels.[24] The efficacy achieved with Candesartan Cilexetil, as reported in reviewed studies [mean 8.7 mmHg in systolic blood pressure (SBP), and 7.1 mmHg in diastolic blood pressure (DBP)], seems favorable compared not only to adult efficacy profile but also to antihypertensive outcomes described in the same general age group of children for other medication treatments including B blockers.[31] Additional published results of Candesartan Cilexetil treatment were restricted to two trials on 17 and 11 children with hypertension or proteinuria; these research demonstrated a systolic and diastolic blood pressure reduction of 9.9 and 7.4/5.9 mmHg, respectively.[20,21]

Valsartan was found to effectively regulate blood pressure in hypertensive children and adolescents aged over six in two well-designed trials. Valsartan effectively and dose-dependently lowered SBP after a few weeks of intervention.[25,27] Regarding the BP lowering property, Valsartan was not inferior to Enalapril after 12 weeks of treatment, and a similar

percentage of Valsartan- and Enalapril-taken by children had a similar mean sitting SBP response.[32] Valsartan treatment for up to 72 weeks was well tolerated.[27]

Regarding the blood pressure lowering effect of Losartan, it was associated with a rapid decrease in all blood pressure measurements in children with hypertension and proteinuria. Over an average follow-up of 2.42 years, diastolic and mean arterial blood pressures (MABP) control were notably well maintained, and glomerular filtration rate (GFR) was conserved with the progression of underlying renal diseases.[22] In a different trial, the response to the dose of losartan from 0.05 mg/kg/d to 2.5 mg/kg/d was also adequately demonstrated.[24] They showed that even low doses of losartan were effective in decreasing blood pressure compared with placebo.[24] In children, a 3- week treatment is sufficient to detect the maximum antihypertensive effects of a given dose of Losartan.[24]

In the United States, Olmesartan Medoxomil is licensed for the management of hypertension in pediatric patients aged 6 to 16 years.[33] Its blood pressure lowering efficacy was established in a 5-week dose-response study in hypertensive patients.[23] In each group, the proportion of children with treatment-related adverse reactions was low, and the low-dose and high-dose active therapy cohorts were similar. Most side effects were mild to moderate in severity and were not believed to be due to the active treatment.[23]

Based on the major endpoint of notable reduction in SBP compared with placebo, Telmisartan at a dose level of 2 mg/kg was found to be an efficient antihypertensive medicine.[25] Authors have discussed that in order to obtain an equal therapeutic effect, pediatric patients require a higher Telmisartan dosing (on an mg/kg basis) compared to adults.[25] The long-term study of Azilsartan efficiency revealed that 63% of patients had reached their goal blood pressure by the end of 12th week.[26] The safety and efficacy profiles were similar to those seen in hypertensive adults taking similar weight-adjusted dosages of Azilsartan.[26] The plasma concentrations of Irbesartan attained with a daily dose of 2 mg/kg lowered blood pressure in a pediatric research work with 23 hypertensive patients.[2]

CONCLUSION

In children aged more than six years and adolescents with essential hypertension, ARBs including Candesartan, Valsartan, Losartan, etc. are effective antihypertensive medications. In this age cohort, safety concerns should also be addressed/taken into consideration.

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