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REVIEW

Nwaiwu O
Olayemi SO
Amao O

Use of angiotensin II receptor blockers in children- a review of evidence

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Nwaiwu O (✉)
Amao O
Department of Pharmacology, Therapeutics & Toxicology, College of Medicine , University of Lagos, Nigeria.
Email: obiyo_nwaiwu@yahoo.com

Olayemi SO
Department of Medicine, Lagos University Teaching Hospital, Idi-Araba, Lagos Nigeria

Abstract: *Background:* The incidence of hypertension in the pediatric population has been increasing. Childhood blood pressure is predictive of adult BP. The renin angiotensin aldosterone system pathway is important in the mediation of pediatric hypertension. New therapies approved for adults are often used off label in children with little or no efficacy and safety data in the paediatric population The angiotensin receptor blockers has been shown to be effective and safe in the treatment of pediatric hypertension.
Objective: The objective of this review is to highlight available clinical evidence on the efficacy, safety tolerability and kinetics of angiotensin receptor blockers in childhood hypertension and its antiproteinuric effect in renal disease.
Method: The search strategy was based on Pubmed, Medline database, Cochrane Library, manual, Google and Yahoo searches. We summarized ten randomized controlled trials (RCTs .The search was done in June 2014 and updated in January and May 2015 in English language .
Results: A total of 120 publications were accessed from which 68 references were included in the review. The design and outcome of ten key randomised trials are summarised. Randomised trials have demonstrated the efficacy of angiotensin receptor blockers in the pediatric population aged 1–16 years. This class of drugs reduce blood pressures in pediatric patients with hypertension and proteinuria in renal disease. Safety pharmacokinetic, dosage, and palatability of adult formulations for the paediatric age group are highlighted
Conclusion: Angiotensin receptor antagonists are useful effective and safe alternatives to available antihypertensive therapy in paediatric population. Angiotensin receptor antagonists should however be prescribed cautiously for sexually active adolescent females due to concern about angiotensin receptor blocker fetopathy.

Keywords: Angiotensin receptor blockers, childhood hypertension, drug safety, drug efficacy, pharmacokinetics and renal diseases.

Introduction

Hypertension is a common disease in adults, with a prevalence which increases with age, ranging from 15% in young adults to 60% in persons over the age of 65 years[1]. Persistent hypertension in children is predominantly secondary and norms for blood pressure in children and adolescents, definitions of hypertension , guidelines for the diagnosis and treatment of hypertension have been published for children aged 2 to 18 years[2].
Globally the prevalence of hypertension in children is on the increase[3] and varies between studies a study in South East Nigeria reported the prevalence of hypertension in adolescents to be 4% with male and female prevalence rates of 3.8% and 6.9% respectively[4]. Children with elevated blood pressure tend to maintain that level of blood pressure into adulthood[5].

Normal blood pressure values, definition of hypertension

In the criteria of the Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents, normal BP in children is defined as systolic blood pressure (SBP) and diastolic blood pressure (DBP) less than 90th percentile for age, sex and height, whereas hypertension is defined as SBP and/or DBP persistently 95th percentile or more, measured on at least three separate occasions with the auscultatory method[2].

The fourth report also provides criteria for staging the severity of hypertension in children and adolescents, and

this is useful clinically to guide evaluation and management(Table1) [2]

Table 1: Definition and classification of hypertension in children and adolescents

Class	SBP and/or DBP Percentile
Normal	<90th
High-normal	≥ 90th to < 95th ≥ 120/80 even if below 90th percentile in adolescents
Stage1 hypertension	95th percentile to the 99th percentile plus 5mmHg
Stage2 hypertension	> 99th percentile plus 5mmHg

Modified from task force on high blood pressure in children & adolescents[2].

The renin-angiotensin-aldosterone system (RAAS)

The renin-angiotensin-aldosterone system (RAAS) plays an important role in the pathogenesis of hypertension in patients of all ages. Angiotensin II, the principal pressor agent of RAAS mediates the effects of an over-active renin-angiotension system such as vasoconstriction and retention of sodium and water which leads to hypertension[6,7]. Plasma concentrations of angiotensin II and aldosterone are largely determined by the level of plasma rennin activity[8]. Renin is secreted by the juxtaglomerular apparatus in response to various stimuli such as a decrease in arterial blood pressure as detected by barareceptors a decrease in sodium levels in the ultrfiltrate of the nephron, and lastly sympathetic nervous system activity, which also controls blood pressure, acting through the $beta_1$ adrenergic receptors.[9]

The angiotensin receptors are a class of G protein coupled receptors with angiotensin II as their ligand[10]. The receptors are responsible for the signal transduction of the vasoconstricting effect of angiotensin II. [11]

Angiotensin II is a very important mediator of progressive renal failure. It is responsible for proteinuria which results from glomerular hyperfiltration due to increased intraglomerular pressure and structural changes to the glomeruli caused by proinflamatory mediators, fibroblast proliferation and production of superoxide free radicals.[12]

Angiotensin II antagonists exerts their blood pressure lowering effects by directly and selectively blocking the activity of angiotensin II on the AT_1 receptor.Angiotensin-II antagonists have been shown to be both well tolerated and effective in lowering blood pressure in adult clinical trials.[10]

Justification for this review

New medicines can result in significant improvements in reducing morbidity and mortality[13]. Drugs approved for adults are often used in children because limited pediatric clinical trials, has led to limited or no pediatric documentation with respect to many drugs approved for adults . This off label use of drugs in children often implies that the dose, dosing frequency, or the age/weight of the patient is not in agreement with drug labeling and includes where a total lack of information in the label about pediatric use of the drug and the use of a non-approved dose in relation to age or weight.[14-17] Concerns has been expressed by different authors about the interpretation of safety data by the pharmaceutical industry in relation to new products. [18,19] This is because many physiologic differences between children and adults may result in age-related changes in pharmacokinetics and pharmacodynamics of drugs. [20,21]Therefore adjusting from adult dosages does not always give correct doses for children .

Reports have highlighted safety concerns regarding the use of angiotensin II receptor blockers in preschool children. Although considered to be unrelated to the investigational drug these reports highlighted the deaths of three preschool children out of the 183 children with hypertension who received valsartan or candesartan in two clinical trials. [22]

The primary objective of this review was to highlight available clinical evidence on the efficacy, safety tolerability and kinetics of angiotensin receptor blockers in childhood hypertension and its antiproteinuric effect in renal disease .

Methods

The search strategy was based on Pubmed, Medline database, Cochrane Library, manual, Google and Yahoo searches. The search was done in English language in June 2014 and updated in January and may 2015. There was no limitation to the year of publication. Search was based on the following keywords : angiotensin receptor blockers, childhood hypertension, drug safety, drug efficacy kinetics, tolerability, renal diseases. randomised clinical trials in pediatric patients with hypertension, and safety of antihypertensive drugs in pregnancy .

Results

A total of 120 publications were accessed from which 68 references were included in the review . Ten key randomised trials are summarised and presented in table 2. Randomised trials have demonstrated the efficacy of angiotensin receptor blockers in the pediatric population aged 1–16 years. This class of drugs reduce blood pressures in pediatric patients with hypertension and proteinuria in renal disease. Safety pharmacokinetic, dosage, issues of paediatric formulations and palatability for the child have been highlighted

Table 2: Study design and treatment outcome of studies conducted with arbs in children

Study	Deisign	Outcome /Conclusion
Lubrano,R et al. [40] *Pediatrics* 2006;118;e833;	A randomized study of 10 children (mean age: 12.3 _ 4.06 years) with proteinuria resulting from chronic renal diseases of various causes.	In the short term, the combination of angiotensin-converting enzyme inhibitors and angiotensin II type 1 receptor antagonists for children with proteinuria of renal origin reduced proteinuria significantly
Meier, CM et al. [63] *Br*JClinPharmacol. 2007 ; 63(5): 628–631.	Taste and smell acceptability of five angiotensin II receptor blockers were compared among 21 nephropathic children using a visual analogue scale palatability score.	From the perspective of the nephropathic child, the taste of pulverized candesartan cilexetil is superior to that of irbesartan,losartan, telmisartan or valsartan
Flynn, JTet al. [52] H*ypertension*. 2008;52:222-228 .	This was a multicenter double-blind, randomized, multicenter study performed at 36 centers	In children _6 years of age, valsartan effectively lowered SBP and diastolic blood pressure compared with placebo. Valsartan treatment had no demonstrable negative effects on growth and development .
Hazan, *L* et al. [35] *Hypertension*. 2010;55:1323-1330.	A randomized, multicenter, double-blind, parallel-group, prospective dose-ranging study in patients 6 to 16 years of age with primary or secondary hypertension	Olmesartan medoxomil was safe and efficacious in children with hypertension, resulting in significant blood pressure reductions.
Webb NJ et al.[39] *Clin J Am Soc Nephro l*2010. 5: 417–424,	12-week, double-blind, multinational study	Losartan significantly lowered proteinuria and was well tolerated after 12 weeks in children aged 1 to 17 years with proteinuria with or without hypertension.
Wells, T. et al. [31] J Clinhypertens2011 ;13(5):357-65.	Children aged 6 to 16 years old with a mean sitting systolic BP (SSBP) _95th percentile for age, sex, and height with documented hypertension were studied in a prospective 4-week,double-blind, randomized,multicenter study	Valsartan appeared to provide dose-dependent reductions in SSBP and SDBP in children with hypertension over a dose range of 0.1 mg⁄kg to 4.6 mg⁄kg (10 mg–160 mg).
Schaefer et al[33] J Hypertens 29:000–000 2011	A 12-week, randomized, double-blind, parallel-group, active-controlled study	Valsartan and enalapril provided comparable BP reductions and effective BP control and were well tolerated in hypertensive children aged 6–17 years.
Wells TG et al [55] Paediatr Drugs 2012 1;14(6):401-9.	An open-label, multicenter, single-dose study was conducted in children and adolescents aged 12 months-16 years with hypertension	Olmesartan medoxomil was well tolerated and demonstrated a pharmacokinetic profile in pediatric patients similar to that of adults when adjusted for body size
Moretti, ME. et al [44] Obstetrics and Gynecology International Volume 2012,	a prospective, observational, controlled cohort study.	inadvertent exposure to ACE inhibitors/ARBs in the first trimester of pregnancy may not present significant risks for malformations in live births but may be associated with higher rates of spontaneous abortion.
Schaefera, F et al[34] J Hypertens2013 31:993–1000	I A multicenter, randomized, double-blind,parallel-group study, 75 patients with a documented history of hypertension	In a dose dependent manner. Valsartan demonstrated significant reductions in BP compared with baseline and provided consistent reductions over26 weeks.

Discussion

Currently, multiple antihypertensive agents are approved for use in children[23]. Data on the use of renin angiotensin system antagonists in the treatment of childhood hypertension are available[24-29]. This review highlights the efficacy, safety tolerability and kinetics of angiotensin receptor blockers in childhood hypertension and its antiproteinuric effect in renal disease .

Efficacy

Two recent trials have demonstrated the efficacy of angiotensin receptor blocker monotherapy in the pediatric population aged 1–16 years. Once-daily oral preparations of valsartan achieve adequate blood pressure con

trol in the pediatric population[30]. In children and adolescents aged 6-16 years significant dose-dependent reductions from baseline in mean sitting systolic BP (msSBP) were observed for recipients of valsartan following 2 weeks' treatment[31]. Compared to enalapril in hypertensive children and adolescents aged 6-17 years, valsartan was no less effective than enalapril in reducing BP. Following 12 weeks' treatment, the least square mean reduction from baseline in mean systolic blood pressure in recipients of valsartan was non-inferior to that in recipients of enalapril and was well tolerated[32,33].

In a multicenter, randomized, double-blind, parallel-group study, 75 patients with a documented history of hypertension were randomized to receive valsartan (0.25, 1 or 4 mg/kg per day) for 6 weeks, then rerandomized to receive placebo or valsartan for 2 weeks. At Week 6, significant reductions in MSSBP ($P<0.05$) from baseline were observed for all three valsartan doses[34].

The efficacy and safety of olmesartan medoxomil in children with hypertension, defined as systolic blood pressure measured at or above the 95th percentile (90th percentile for patients with diabetes, glomerular kidney disease, or family history of hypertension) for age, gender, and height while off any antihypertensive medication current was investigated. Efficacy results showed a dose-dependent, statistically significant reduction in seated trough systolic and diastolic blood pressure. The olmesartan medoxomil dose response remained statistically significant when adjusted for body weight. Olmesartan medoxomil was safe and efficacious in children with hypertension, resulting in significant blood pressure reductions[35].

Regardless of underlying aetiology, the presence of hypertension is associated with cardiovascular morbidity and progressive kidney injury[36]. In the Chronic Kidney Disease in Children study, 37% of children with chronic kidney disease were diagnosed with elevated BP, and yet 39% of these were not receiving antihypertensive medication[37].

The use of Angiotensin II receptor blockers is largely established in adult patients with kidney disease because, like converting enzyme inhibitors, they are more effective than most other antihypertensive drugs in slowing the progression towards end-stage kidney disease[38].

A subgroup analysis of a 12-week, double-blind study demonstrated that losartan significantly lowered proteinuria versus placebo and amlodipine and was well tolerated in children (1-17 years old) with proteinuria secondary to Alport syndrome. Losartan maintained proteinuria reduction, and enalapril produced a further proteinuria reduction over the 3-year study period. Both agents were generally well tolerated. ·ARAs can be considered effective and safe in lowering BP and proteinuria in the pediatric age group[39].

A study enrolled 10 children (mean age: 12.3 _ 4.06 years) with proteinuria resulting from chronic renal diseases of various causes and investigated whether the combination of an angiotensin-converting enzyme inhibitor and an angiotensin II type 1 receptor antagonist offers better control of proteinuria and cardiovascular parameters without causing adverse side effects. In the short term, the combination of angiotensin-converting enzyme inhibitors and angiotensin II type 1 receptor antagonists for children with proteinuria of renal origin reduced proteinuria significantly, compared with baseline or either drug alone. Furthermore, echocardiographic studies gave evidence of reduction of left ventricular hypertrophy. Additional studies will evaluate long-term results[40].

Safety and tolerability

There are very few data on the safety of antihypertensive drugs in pregnancy .[41] Generally the class of angiotensin II receptor blockers (ARBs) has proved to be better tolerated than other leading classes of antihypertensive agents[42,43].

Exposure to angiotensin II receptor blockers during the second part of pregnancy can lead to reduced fetal kidney perfusion that may result in oligoamnios and neonatal renal insufficiency, and these are similar to abnormalities observed after exposure to angiotensin-converting enzyme inhibitors[44], Intrauterine growth restriction, prematurity, patent ductus arteriosus, severe neonatal hypotension, neonatal anuria, and neonatal or fetal death have also been observed with these drugs . Anuria associated with oligohydramnios may produce fetal limb contractures, craniofacial deformities,and pulmonary hypoplasia[45,46].

Although published cohort studies and series [41,44,46-50] showed different malformation rates after first trimester exposure to ACE inhibitors/ARBs, angiotensin II receptor blockers should be avoided in pregnancy. However if these agents are prescribed accidentally to a pregnant woman, monitoring of amniotic fluid volume and beta^2-microglobulin fetal blood levels after discontinuation of the AT1 antagonist can provide critical data for advising parents on pregnancy and fetal outcome[43]. In a study there were no differences in rates of major malformations. Both the ACE-ARBs and disease-matched groups exhibited significantly lower birth weight and gestational ages than the healthy controls (P <0.001 for both variables). There was a significantly higher rate of miscarriage noted in the ACE/ARB group (P <0.001). These results suggest that ACE inhibitors/ARBs are not major human teratogens; however, they may be associated with an increased risk for miscarriage [45].

A trial of angiotensin II receptor blockers (ARBs) was performed in children 0-5 years of age. Three deaths occurred in the 183 (1.6%) hypertensive children participating in the two trials. At least two of these deaths occurred in children known to be susceptible to drugs acting on the renin-angiotensin system, that is, children with ongoing nephrotic syndrome and acute gastroenteritis. Clinicians who prescribe ARBs in preschool children need to be aware of the risk of drug toxicity especially in children susceptible to intravascular dehydration. Clinicians should consider discontinuing the drugs in the presence of acute diarrhoea[51].

The efficacy and safety of valsartan were studied in 90 children (mean age: 3.2 years; 60% male; 30% black) with systolic blood pressure (SBP) _95th percentile. Nineteen percent received valsartan in addition to previous antihypertensive therapy. Adverse events were minor and serious adverse events and drug-related adverse events occurred infrequently .Valsartan treatment had no demonstrable negative effects on growth and development. [52]

The safety of valsartan were studied in 90 children (mean age: 3.2 years; 60% male; 30% black) with systolic blood pressure (SBP) ≥95th percentile. Adverse events were minor and occurred at similar frequencies in both the valsartan and placebo arms . All of the valsartan doses evaluated in studies were well tolerated. The majority of adverse events were mild or moderate and transient in nature, the most frequent being cough, fever, upper respiratory infection, and diarrhea and are similar to findings in other clinical trials of antihypertensive medications conducted in older children[53,54]

Pharmacokinetics

An open-label, multicenter, single-dose study characterized the pharmacokinetics and short-term safety of olmesartan medoxomil in children and adolescents aged 12 months-16 years with hypertension. Olmesartan medoxomil was well tolerated and demonstrated a pharmacokinetic profile in pediatric patients similar to that of adults when adjusted for body size[55]. Losartan unlike valsartan , requires oxidative transformation to the active compound . [56] In children, plasma valsartan levels peak at two hours after oral administration and subsequently reduce in a biexponential manner. [57] The plasma half-life is about four hours in children under six years of age. In children aged 6–12 years, the plasma half-life is about five hours. [57] Clearance is not significantly affected by age after correcting for fat free body mass. The rate of clearance is 0.076–0.098 L/hour/kg in children aged 1–16 years. No significant dosage adjustment is needed in mild to moderate kidney or liver disease. [56,57]

Dosage and palatability

Currently available data indicate that extrapolating adult doses of the angiotensin antagonists, valsartan[58], irbesartan[59], losartan[60] and, candesartan [61] is safe and effective in treating children with arterial hypertension or proteinuria.

A dose response study in children aged 6–16 years demonstrated that valsartan was efficacious and well tolerated in doses ranging from 10 to 160mg (0.1–4.6 mg/kg)[31,52]. The recommended dosage of valsartan for treating hypertension in the pediatric population is 1.3–2.7 mg/kg, with a starting dose of 1.3 mg/kg[62]. This amounts to a starting dose of 40 mg in children below 35 kg and 20 mg for children below 15 kg. Doses 160 mg (4.7 mg/kg) have not been tested in children and may not be recommended[44].

In another study patients aged <6 years received an oral suspension of olmesartan medoxomil at a dose of 0.3 mg/kg of bodyweight (not to exceed 20 mg), those aged ≥6 years who weighed ≥35 kg received olmesartan medoxomil 40 mg tablets, and those who weighed <35 kg received olmesartan medoxomil 20 mg tablets. [55]

Lack of paediatric formulations such as suspensions or other age-appropriate drug formulations for drugs originally designed for use in adults, is a major barrier to the use of angiotensin antagonists in drug therapy of hypertension in children and palatability of the medication is crucial for adherence to prescribed drug regimen[63]. From the perspective of the child with kidney disease, the taste of pulverized candesartan measured by means of a visual analogue scale the palatability score. Is significantly superior to that of pulverized irbesartan, losartan, telmisartan or valsartan[63]. Tablets are crushed by parents and administered mixed with solid food or a palatable drink[64,65]. An extemporaneously formulated solution of valsartan can be prepared for children who are unable to swallow commercially available tablets[52]

Generally angiotensin receptor blockers can be used as monotherapy or as fixed dose combinations[66]. The combination of a diuretic and an angiotensin receptor blocker works well because diuretics induce reflex activation of the renin angiotensin system potentiating the action of renin angiotensin system blockers. The combination of a renin angiotensin system blocker and a calcium channel blocker (CCB) has also been widely used in adults and these agents also have complementary actions. [67,68]

Conclusion

Angiotensin II receptor blockers selectively block the angiotensin type I receptor. Given its effects on angiotensin blockade, angiotensin II receptor blockers reduce blood pressure in hypertension and proteinuria in kidney disease. For these reasons, and good safety and tolerability profile, angiotensin II receptor blockers are an attractive drug for use in children with hypertension. However angiotensin receptor antagonists should be prescribed cautiously for sexually active adolescent females due to concern about angiotensin receptor blocker fetopathy.

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