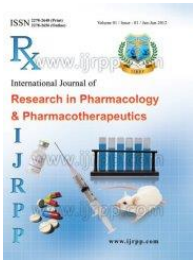
International Journal of Research in Pharmacology & Pharmacotherapeutics



ISSN Print: 2278-2648 ***IJRPP |Vol.7 | Issue 4 | Oct - Dec - 2018***
ISSN Online: 2278-2656 ***Journal Home page: www.ijrpp.com***

Research article ***Open Access***

Losartan in management of hypertension in children

Dr. S. Umamaheswara Raju[1], Dr. J. Margaret Viola[2*], Dr P. Raghunadha Rao[3]

[1]*Associate Professor, Department Of Pharmacology, Gandhi Medical College, Hyderabad, Telangana.*
[2]*Associate Professor, Department Of Pharmacology, Gandhi Medical College, Hyderabad, Telangana.*
[3]*Assistant Professor, Department Of Pharmacology, Gandhi Medical College, Hyderabad, Telangana.*
***Corresponding author: Dr. J. Margaret Viola**

ABSTRACT

Background

An increasing number of healthy children and adolescents across the world are being diagnosed with hypertension, which is an emerging problem that no pediatrician can afford to ignore. Hypertension in children is defined as systolic BP (SBP) and/or diastolic BP (DBP) ≥95th percentile for sex, age, and height on ≥3 occasions. It occurs in 1%–10% of children and adolescents and, at younger ages, frequently has a cardiac or renal cause. Losartan, an Angiotensin II Receptor Blocker (ARB), is an antihypertensive therapy with demonstrated benefit in children.

Objectives

Once-daily Losartan reduces Blood Pressure in a dose-dependent manner and is well tolerated in hypertensive children aged 6–16 years. This study assessed the dose-response relationship, safety, and tolerability of Losartan in hypertensive children aged 61 year to 5 years.

Design

This was a 10-week, randomized, open-label, dose-ranging study.

Duration

One year (November 2016 - December 2017)

Setting

Gandhi Medical College, Hyderabad.

Participants

Sixty patients diagnosed at Gandhi Medical College, Hyderabad.

Methods

Patients were randomized to Losartan at the following dosages: 0.1 mg/kg per day (low), 0.3 mg/kg per day (medium), or 0.7 mg/kg per day (high). Losartan was titrated to the next dose level (to a 1.4 mg/kg per day maximum dosage, not exceeding 100 mg/d, which was not one of the three original doses offered at randomization) at weeks 3, 6, and 9 for patients who did not attain their goal BP and were not taking the highest dose. Dose response was evaluated by analyzing the slope of change in sitting systolic BP (SBP; primary end point) and diastolic BP (DBP; secondary end point) after 3 weeks compared with baseline. Adverse events (AEs) were recorded throughout.

Results

Mean sitting BP decreased from baseline in the low, medium, and high-dose groups by 7.2, 7.4, and 6.8 mmHg, respectively, for SBP and 8.0, 5.2, and 6.7 mmHg, respectively, for DBP after 3 weeks. No dose-response relationship was established by the slope analysis on SBP (P=0.74) or DBP (P=0.63). The BP-lowering effect was observed throughout the one year extension.

Conclusions

Hypertensive children aged 1 year to 6 years treated with Losartan 0.1–0.7 mg/kg per day had clinically significant decreases from baseline in SBP and DBP, yet no dose-response relationship was evident. Losartan, at a dosage up to 1.5 mg/kg per day, was well tolerated.

Keywords: Hypertension, Children, Management, ARB, Losartan.

INTRODUCTION

Systemic hypertension is an important condition in childhood, with estimated population prevalence of 1-2% in the developed countries. Nutritional surveys, in the India show a significant secular increase in systolic and diastolic blood pressures. The causes for increase in blood pressure are attributed to obesity, change in dietary habits, decreased physical activity and increasing stress. Small surveys in school children suggest a prevalence ranging from 2-5 %. Elevated blood pressure, systolic or diastolic at any age, in either sex is a contributor for all forms of cardiovascular disease. Identifying and modifying risk factors reduces the incidence and complications in adolescents and adult. Prevalence of hypertension varies across countries and states. It is multifactorial disease, influenced by genetic, racial, geographic, cultural and dietary patterns. Hypertension in children is defined as systolic BP (SBP) and/or diastolic BP (DBP) ≥95th percentile for sex, age, and height on ≥3 occasions. Current guidelines state that the goal of therapy is to reduce both SBP and DBP to, 95th percentile, or to, 90th percentile in the presence of comorbidities or end organ dam-age, and treatment should progress to the highest recommended dose until the goal is achieved. Losartan, an Angiotensin II Receptor Blocker (ARB), is an antihypertensive therapy with demonstrated benefit in children. In children aged 1 month to 16 years, the pharmacokinetic parameters of Losartan and its active metabolite E-3174 were similar across all age groups after oral administration, and treatment was well tolerated. A randomized, double-blind study showed that once-daily Losartan reduced BP in a dose-dependent manner and was well tolerated in hypertensive children aged 6–16 years. This randomized clinical study explored the dose-response relationship and the safety and tolerability of Losartan in hypertensive children aged 1 year to 6 years.

MATERIALS AND METHODS

This was a 10-week, randomized, open-label, parallel-group, dose-ranging study of Losartan in young children with either newly diagnosed, therapy naïve hypertension or those with inadequate BP control with their current or past antihypertensive regimen. Patients taking other antihypertensive therapies (including angiotensin-converting enzyme inhibitors) before screening did not have a washout period; Losartan was added to their existing regimen. Boys and girls aged 1 year to 6 years were enrolled. For children aged ≥1 year, hypertension is defined as SBP ≥95th percentile according to charts based on sex and age from the Report of the Second Task Force on Blood Pressure Control in Children. Patients with SBP and/or DBP ≥90th percentile and evidence of end organ damage (left ventricular hypertrophy, retinal vascular changes, etc.) or comorbidities (CKD, overweight [≥95th percentile for age], hyperlipidemia, or diabetes mellitus) may have been enrolled at the investigator's discretion. Patients were required to have an eGFR ≥30 ml/min per 1.74 m^2 calculated by the Schwartz formula based on the baseline plasma creatinine value. All patients were randomly allocated to open-label Losartan, starting at the following dosages: 0.1 mg/kg per day (low), 0.3 mg/kg per day (medium), or 0.7 mg/kg per day (high) via an interactive voice response system. All doses were supplied as Losartan dry powder in a sachet formulation for in situ reconstitution as a suspension. The study did not include a placebo or

comparator treatment group. Patients were stratified by the presence of comorbidities or evidence of end organ damage that warranted a lower BP goal. The stratification was accomplished by the interactive voice response system. Losartan was titrated to the next dose level (up to a maximum dosage of 1.4 mg/kg per day, not to exceed 100 mg/d, which was not one of the three original doses offered at randomization) at weeks 3, 6, and 9 for patients who did not attain their goal BP and were not tak-ing the highest dose. With the exception of another ARB, investigators were permitted to add and titrate other open-label antihypertensive medications (including angiotensin-converting enzyme inhibitors) for children who reached 1.4 mg/kg per day of Losartan and did not attain goal BP. Sitting BP (or supine BP if the child could not sit) was monitored at each visit using a standardized oscillometric BP device. The primary efficacy end point was the slope of change in sitting SBP after the first 3 weeks of treatment compared with baseline as a function of dose, and the principal secondary efficacy end point was the slope of change in sitting DBP using the same parameters. Exploratory end points included the change from baseline in SBP and DBP at 3-week intervals (base phase), as well as the percentages of patients who attained goal SBP or DBP by week 3. Changes from baseline in SBP by week 3 were evaluated for pre-specified subgroups defined by sex, age (<1 year or ≥1 year), race, prior use of antihypertensive medication (yes or no), presence of comorbidities/end organ damage (yes or no), and position during BP measurement (sitting or supine).

OBSERVATIONS AND RESULTS

Baseline characteristics were generally similar between the treatment groups (Table 1).

Table 1: Baseline characteristics of patients.

Characteristic	Dosage Per Day			Total
	Low (0.1 Mg/Kg)	Medium (0.3 Mg/Kg)	High (0.7 Mg/Kg)	
Participants(N)	19	20	21	60
Sex				
Boys	11	12	11	34
Girls	8	8	10	26
Duration Of Hypertension(Months)				
Median	4.0	3.0	4.0	3.0
25^{th}&75^{th} Percentile	1-8	1-9	1-9	1-9
Antihypertensive Medication	6	8	9	22
Agents Acting On RAS	2	3	2	7
Calcium Channel Blockers	1	2	3	6
B-Blocking Agents	1	1	2	4
Diuretics	2	1	1	4
Other Antihypertensives	0	1	1	2
DBP				
Mean(SD)	67.9	68.1	68.6	68.4
Range	55-83	56-81	58-87	57-84
SBP				
Mean(SD)	112.1	113.9	114.5	113.6
Range	90-129	100-130	102-134	91-131

Blood Pressure

Reductions from baseline to week 3 in mean sitting SBP and DBP were observed in all dose groups. No dose-response relationships were established by the slope analysis on SBP or DBP. The estimated slopes of dose for change from baseline were 1.2 mmHg/mg per kg per dayfor SBP and 1.8 mmHg/mg per kg per day for DBP. Consistent changes from baseline in SBP during the 10-week base phase were observed in the medium-dose group as follows: 27.2, 27.8, 29.3, mmHg at weeks 3, 6, 9, respectively. Consistent changes were

also observed in the low and high-dose groups through week 9. Consistent changes from baseline in DBP dur-ing the 10-week base phase were observed overall, but no consistent changes were observed at the 3-week intervals within each dose group. By week 3, 51.5% reached their goal BP. Four patients required additional antihypertensive medication during the 10-week base phase (0 in the low, 2 in the medium, and 2 in the high-dose groups). The changes rom baseline in BP were similar across all patient sub-groups examined, and suggested no trend toward a dose response.

Table 2. Summary of change from baseline in SBP and DBP as a function of dose

BP(mg/Kg/day)	n	Baseline	Week 3	Change From Baseline
SBP				
Low (0.1)	19	112.1	104.9	7.2
Medium (0.3)	20	113.9	106.5	7.4
High (0.7)	21	114.5	107.7	6.8
DBP				
Low (0.1)	19	67.9	59.9	8.0
Medium (0.3)	20	68.1	62.9	5.2
High (0.7)	21	68.6	61.9	6.7

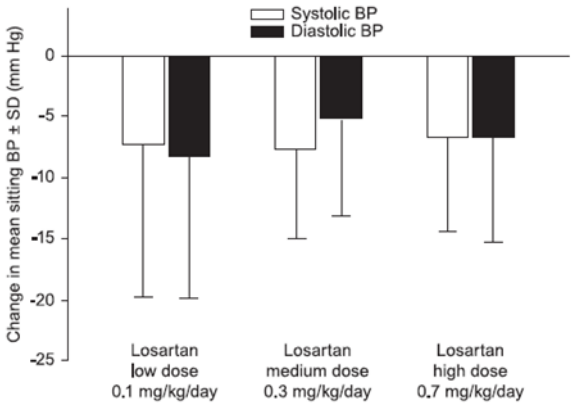


Fig 1. Change from baseline to week 3±SD in mean systolic BP and diastolic BP in the base study.

Safety

Table 3 provides a summary of AEs during the 10 weeks of the study by dose received (low, medium, high, and highest [1.4 mg/kg per day]) at the time of the event.

Table 3. Adverse Effects summary by dose received at time of event over 10 weeks

Adverse Effect Type	Dosage Per Day				Total
	Low (0.1 Mg/Kg)	Medium (0.3 Mg/Kg)	High (0.7 Mg/Kg)	Highest (1.4 Mg/Kg)	
Participants(N)	19	20	21	21	100
Clinical					
Any Clinical AE	8	6	7	9	21
Any Drug-Related Clinical AE	0	1	1	1	3
Any Serious Clinical AE	2	1	2	0	5
Any Serious Drug-Related Clinical AE	0	0	0	0	0
Died	0	0	0	0	0

Cause Of Discontinuation Of Study Medication					
Clinical AE	0	0	0	0	0
Clinical Drug-Related AE	0	0	0	0	0
Serious Clinical AE	0	0	0	0	0
Serious Drug-Related Clinical AE	0	0	0	0	0
Laboratory					
Any Laboratory AE	1	1	0	0	2
Any Drug-Related Laboratory AE	0	0	1	0	1
Any Serious Laboratory AE	0	0	0	0	0
Any Serious Drug-Related Laboratory AE	0	0	0	0	0
Died	0	0	0	0	0
Cause Of Discontinuation Of Study Medication					
Laboratory AE	0	0	0	0	0
Laboratory Drug-Related AE	0	0	0	0	0
Serious Laboratory AE	0	0	0	0	0
Serious Drug-Related Laboratory AE	0	0	0	0	0

DISCUSSION

This study is one of the largest antihypertensive medication trials in children aged 1 years to 6 years, a cohort whose BP may be difficult to control and who would benefit from having access to an ARB. Treatment with Losartan produced clinically meaningful decreases from baseline to week 3 in SBP and DBP across all dose groups. No linear dose response for BP was observed at 3 weeks between the low-dose versus the medium-dose or high-dose regimens. This finding is discordant with data from a study of Losartanin older children (aged6–16 years), showing a dose response in the medium-dose (0.75 mg/kg) and high-dose (1.44 mg/kg) regimens compared with the low-dose regimen (0.07 mg/kg) after 3 weeks. The absence of a dose response could not be explained by the addition of antihypertensive therapies to control BP, because no meaningful differences were observed across dose groups. One explanation may be that very young children, particularly those with renal causes of their hypertension, may be more sensitive to the effects of ARBs, and the dosages used here represent the upper end of the dose-response curve. Similar results were reported in a study of the ARB Valsartan in 90 children aged 1–6years. The authors of this study suggested that young children may be uniquely sensitive to treatment, and a lower starting dose might have facilitated demonstration of a dose response. Renin levels are higher in younger children, possibly contributing to greater sensitivity to renin-angiotensin-aldosterone system blockade; however, this association could not be tested because renin was not measured in the present study. One interpretation is that all Losartan doses were equally effective in lowering BP; however, the absence of a placebo arm is an important limitation that must be considered. Nonetheless, it is unlikely that placebo would produce a persistent antihypertensive effect throughout the 10-week phase in these children, who predominantly had a primary renal cause of their hypertension. Considering the statistically significant antihypertensive efficacy of Losartan in older children, coupled with the BP-lowering effects observed in children aged 1–6 years with valsartan, it is reasonable to conclude that despite the lack of a dose response, Losartan lowers BP in children aged 6 years. To permit a relevant risk assessment by drug exposure, AEs were summarized for the actual Losartan dose received at the time of the event, not for the originally randomized dose. All Losartan doses were generally well tolerated. The majority of clinical AEs were reflective of the routine illnesses

experienced in young children or related to the underlying cause of their hypertension, especially recurrent urinary tract infections. The safety profile is consistent with studies of Losartan in older children with hypertension and CKD. The safety profile was similar in the young cohort to that of the overall population, except that the six AESIs observed over the entire treatment period occurred in this subgroup. Although the results from this small group should be interpreted with caution, physicians should closely monitor very young children during treatment with Losartan.

CONCLUSIONS

In conclusion, Losartan produced a consistent BP-lowering effect across all doses examined throughout the phases of this study in hypertensive children aged 1 year to 6 years. No dose-response effect was observed during the first 3 weeks of Losartan therapy. Losartan was generally well tolerated at doses up to 1.4 mg/kg, extending its previously established safety profile to young children.

REFERENCES

[1]. Sinaiko AR: Hypertension in children. N Engl J Med 335, 1968, 1973, 1996

[2]. Flynn JT, Meyers KE, Neto JP, de Paula Meneses R, Zurowska A, Bagga A, Mattheyse L, Shi V, Gupte J, Solar-Yohay S, Han G; Pediatric Valsartan Study Group: Efficacy and safety of the an-giotensin receptor blocker valsartan in children with hyperten-sion aged 1 to 5 years. Hypertension 52, 2008, 222–228.

[3]. Mitsnefes M, Ho PL, McEnery PT: Hypertension and progres-sion of chronic renal insufficiency in children: A report of the North American Pediatric Renal Transplant Cooperative Study (NAPRTCS). J Am Soc Nephrol 14, 2003, 2618–2622.

[4]. National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents: The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents. Pediatrics 114[2], 2004, 555–576.

[5]. Schwartz GJ, Haycock GB, Edelmann CM Jr, Spitzer A: A simple estimate of glomerular filtration rate in children derived from body length and plasma creatinine. Pediatrics 58, 1976, 259–263.

[6]. Broughton Pipkin F, Smales OR, O'Callaghan M: Renin and an-giotensin levels in children. Arch Dis Child 56, 1981, 298–302.

[7]. Hahn L. The relation of blood pressure to weight, height and body surface area in school boys. Arch Dis Child. 27, 1952, 43–53

[8]. Orchard TP, Hedley AJ, Mitchell JR. The distribution and associations of blood pressure in an adolescent population. J Epidemiol Community Health. 36, 1982, 35–42

[9]. Gupta AK, Ahmed AJ. Normal blood pressure and evaluation of sustained blood pressure and evaluation of sustained blood pressure elevation in childhood. Indian Pediatr. 27, 1990, 33–42

[10]. Verma M, Chhatwal J, George SM. obesity and hypertension in children. Indian Pediatr. 1, 1994, 1065–9

[11]. Loria D, Sharma M, Diwedi V, Belapurkar KM, Mathur PS. Profile of blood Pressure in normal school children. Indian Pediatr. 26, 1989, 531–6

[12]. Aggarwal VK, Sharon R, Srivastava AK, Kumar P, Pandey CM. Blood Pressure profile in children of age 3-15 years. Indian Pediatr. 20, 1983, 921–5

[13]. Burke GL, Cresanta JL, Shear CL, Miner MH, Berenson GS. Cardiovascular risk factors and their modification in children. Cardiol Clin. 4, 1986, 33–6

[14]. Jackson LV, Thalange NK, Cole TJ. Blood pressure centiles for Great Britain. Arch Dis Child. 92, 2007, 298–303

[15]. Irgil E, Erkenci Y, Ayetekin N, Ayetekin H. prevalence of hypertension in School children aged 13-18 yrs in Gemlike, Turkey. Euro J Public Health. 40, 1998, 176–8.

[16]. Ng'andu NH. Blood pressure levels of Zambian rural adolescents and their.Relationship to age, sex, weight, height and three weights for height indices. Int J Epidemiol. 21, 1992, 246–52

[17]. Dannenberg AL, Garrison RJ, Kennel WB. Incidence of hypertension in the Framingham study. Am J Public Health. 78, 1998, 676–9

[18]. Thakor HG, Kumar P, Desai VK. An epidemiological study of hypertension amongst children from various primary schools of Surat city. Indian J Community Med. 23, 1998, 110–5
[19]. Torok E, Gyrafas I, Csukas M. Factors associated with stable high blood Pressure in adolescents. J Hypertens. 3(3), 1985, 389–90
[20]. Aullen JP. Obesity, hypertension and their relationship in children and adolescents.An epidemiological study in schools (Authors transl) Sem Hop. 54, 1978, 637–43
[21]. Hardy R, Wadsworth ME, Langenberg C, Kuh D. Birth weight, childhood growth and blood pressure at 43 yrs in a British birth cohort. Int J Epidemiol. 33, 2004, 121–9
[22]. Andriska J, Gombik M, Breyer H, Tarr A. Hypertension in children and adolescents.Results of a long term follow up study 1975-1985. Clin Exp Hypertens A. 8, 1986, 567–9
[23]. Lascaux-Lefebvre V, Ruidavets J, Arveiler D, Amouyel P, Haas B, Cottel D, et al. Influence of parental history of hypertension on blood pressure. J Hum Hypertens. 3, 1999, 631–6.