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K.B. Tallian · M.C. Nahata · M.A. Turman
J.D. Mahan · J.R. Hayes · M.I. Mentser

Efficacy of amlodipine in pediatric patients with hypertension

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Abstract We designed a study to determine the efficacy and safety of amlodipine given once daily in the pediatric population. Twenty-one patients (mean age 13.1 years) with either essential (*n*=160) or renal (*n*=5) hypertension, and newly diagnosed (*n*=15) or poorly controlled or intolerant on existing antihypertensive therapy (*n*=6), were included. Patients received amlodipine once daily at a starting mean dose of 0.07±0.04 mg/kg per day. The total daily dose of amlodipine was increased 25%–50% every 5–7 days if the mean home blood pressure measurements (HBPM) were above the 95th percentile for age and gender. A baseline followed by a repeat 24-h ambulatory blood pressure monitor study (ABPM) was performed in 20 patients when the mean HBPM was below the 95th percentile goal. The mean titrated dose required to control BP was 0.29±0.11 mg/kg per day for those <13 years, 0.16±0.11 mg/kg per day for those ≥13 years, 0.23±0.14 mg/kg per day for essential, hypertension and 0.24±0.13 mg/kg per day for renal hypertension. The ABPM demonstrated that amlodipine provided effective BP control as primary therapy in 14 essential patients. Adverse effects included fatigue (*n*=6), headache (*n*=5), facial flushing (*n*=4), dizziness (*n*=3), edema (*n*=3), abdominal pain (*n*=3), chest pain (*n*=2), nausea (*n*=1), and vomiting (*n*=1). Quality of life appeared to improve during therapy. Amlodipine was an effective once daily antihypertensive agent with an acceptable safety profile. Higher doses of amlodipine were required for younger patients, and monotherapy was effective in patients with essential hypertension.

Key words Amlodipine · Hypertension · Ambulatory blood pressure · Quality of life

K.B. Tallian (✉)
College of Pharmacy, Western University of Health Sciences,
309 East 2nd Street, Pomona, CA 91766-1889, USA
Fax: +1-909-469-5539

M.C. Nahata
College of Pharmacy,
Ohio State University and Wexner Institute for Pediatric Research,
Children's Hospital, Columbus, Ohio, USA

M.A. Turman · J.D. Mahan · M.I. Mentser
Department of Pediatric Nephrology,
Ohio State University and Wexner Institute for Pediatric Research,
Children's Hospital, Columbus, Ohio, USA

J.R. Hayes
Department of Statistics, Wexner Institute for Pediatric Research,
Children's Hospital, Columbus, Ohio, USA

Introduction

Experience with antihypertensive agents is limited in children, since very few drugs are studied in this age group prior to approval for marketing by the Food and Drug Administration. Data in children are usually obtained during clinical use, with initial doses determined by extrapolation from adult doses. Adverse effects may be similar in adults and children, but this is often never verified until enough pediatric experience has accumulated.

Two classes of antihypertensive agents are used widely in children because of their clinical effectiveness and low incidence of adverse effects: angiotensin converting enzyme inhibitors and calcium channel antagonists [1, 2]. Angiotensin converting enzyme inhibitors, including captopril and enalapril, have been used in neonates and children with minimal side effects and effective blood pressure (BP) control [3, 4]. Captopril requires two or three times daily administration [1]. Enalapril, however, has a longer duration of action than captopril, allowing daily or twice daily dosing.

There are three classes of calcium channel antagonists [5]. The phenylalkylamine and benzothiazepine derivatives such as verapamil and diltiazem, respectively, have direct cardiac as well as antihypertensive effects, and are often prescribed for adults when additional benefits outweigh potential adverse effects. These classes of calcium channel antagonists are rarely used to treat pediatric patients with hypertension. Nifedipine, a 1,4-dihydropyridine derivative, has been used to treat pediatric patients with hypertensive emergencies [6]. Major disadvantages of nifedipine and other 1,4-dihydropyridine derivatives,

such as isradipine and nicardipine, are a short duration of action, multiple daily dosing requirements, even with sustained release products, and inconvenient formulations for children.

Amlodipine is a 1,4-dihydropyridine derivative calcium channel antagonist. As with other calcium channel antagonists, amlodipine inhibits voltage-dependent calcium channels in vascular smooth muscle cells and cardiac muscle cells, which prevents the influx of calcium across cell membranes [5, 7]. Although amlodipine has not been studied in children, it has been approved for use in adults with hypertension and angina [7].

Amlodipine appears to offer several advantages over other calcium channel antagonists, which may be relevant for treating hypertension in pediatric patients. Unlike nifedipine, nicardipine, and isradipine, amlodipine is formulated as a nonsustained release tablet, which can be divided without destroying the integrity of the dosage form. Amlodipine has the longest estimation half-life of approximately 36–45 h compared with other calcium channel antagonists [7].

Amlodipine has been reported to have a lower incidence of adverse effects compared with other calcium channel antagonists [8, 9]. This phenomenon may be explained, in part, by the fact that its peak serum concentration (C_{max}) is lower and rises slowly, a high C_{max} has been implicated in the development of vasodilator side effects (i.e., headache, facial flusing, and dizziness) [8]. In a multicenter, general practice study, nifedipine led to a significantly greater incidence of flushing and headache than amlodipine, although no significant difference in peripheral edema was observed [9].

Amlodipine does not appear to significantly interact with most drugs. Cimetidine, known to decrease the metabolism of certain drugs, did not influence the pharmacokinetics of amlodipine upon concomitant administration [10]. Amlodipine had no significant effect on the pharmacokinetics of thiazide diuretics, beta-blockers, angiotensin converting enzyme inhibitors, long-acting nitrates, cimetidine, sublingual nitroglycerin, warfarin, nonsteroidal anti-inflammatory drugs, antibiotics, and oral hypoglycemic drugs [7, 11]. Conflicting reports of an interaction between amlodipine and cyclosporin A (CSA) have been published [12, 13].

A recently published retrospective study described the efficacy of amlodipine in 15 pediatric bone marrow transplant patients with hypertension [14]. BP was measured six times per day using either a Dinamap monitor or an electrocardiogram unit. Amlodipine at a mean maximum dose of 0.16 mg/kg per day significantly reduced both systolic and diastolic BP compared with baseline (6.5±2.7 mm Hg and 5.9±2.7 mm Hg, respectively, $P<0.05$). Ankle edema was found to be a limiting adverse effect of amlodipine in 2 patients, leading to its discontinuation in both cases.

There are no published studies that prospectively describe the efficacy of amlodipine in pediatric patients with hypertension. This led us to design a prospective study to evaluate the efficacy and safety of once daily amlodipine in children with hypertension.

Patients and methods

Study design

The protocol was approved by our institutional review board, and written informed consent was obtained from a parent or legal guardian. Patients were enrolled at Children's Hospital Columbus, Ohio from July 1995 to June 1996 if they fulfilled the following criteria: age between 1 and 18 years, diagnosis of hypertension, defined as a BP >95th percentile for age and gender on three separate occasions, confirmation of hypertension diagnosis by a 24-h ambulatory blood pressure monitor (ABPM, Space Labs Models 90202 and 90207, Redmond, Wash., USA) with BP measured at 20-min intervals at the time of enrollment. Amlodipine was initiated as primary therapy in newly diagnosed patients, or substituted for/added to poorly controlled or intolerant existing therapy. A low-salt, low-fat, and caffeine-free diet in conjunction with regular exercise was encouraged. Patients were excluded if they had cardiovascular contraindications, hypersenstivity to other calcium channel antagonists, necessity of immediate hypertensive control, or pregnancy.

The patient's age, gender, height, actual body weight, body mass index, ethnicity, diagnosis, previous and current medication regimens, and allergies were recorded. Complete blood count and differential, chemistry profile, and urinalysis were measured at baseline and repeated, usually at 3-month intervals.

Drug administration

Amlodipine dose was delivered by either commercially available tablets (2.5, 5, 10 mg) or powder prepared by crushing a tablet to provide a weight-specific dose. The initial dose was based on the actual weight of the patient in kilograms: 5 mg daily if >70 kg, 2.5 mg daily if 50–70 kg, and 0.05 mg/kd per day if <50 kg. The initial once daily dose was administered orally on awakening. The dose of amlodipine was increased by 25%–50% with doses rounded to the nearest 2.5 mg every 5–7 days if the average home blood pressure values (HBP) were above the 95th, percentile for age and gender of the patient. When the average HBP was <95th, percentile, patients were remonitored by ABPM. The dose was again increased if the ABPM indicated inadequate BP control over 24 h. This titration schedule was followed until BP control was achieved or until a dose of 0.5 mg/kg per day was reached. When a maximum dose of amlodipine was reached, a second antihypertensive agent was added if needed. If clinically significant adverse effects or possible toxicity was detected, the dose of amlodipine was reduced of discontinued, depending on the severity of the observation.

Measurements

Patients were provided with a sphygmomanometer and BP cuff. Patients requiring a small BP cuff received a manual system (Starline, Richmond, Va., USA) and those requiring a large BP cuff received a digital system (Moron model HEM-412C, Vernon Hills, Ill., USA). At the time of enrollment, patients and caregivers were instructed about the proper method to measure BP and heart rate.

Patients or caregivers measured BP twice daily on the right arm in the sitting position. BP readings were recorded in a BP diary. Patients were contacted twice weekly by telephone to obtain BP readings and were also followed, usually monthly, at the Nephrology Outpatient Clinic.

Adverse effects

Patients were monitored by bi-weekly telephone interviews, questionaires, and office visits for the presence or absence of headache, dizziness, nausea, vomiting, swelling, constipation, chest pain, cognitive changes, or other events during the study. Events were rated based on a severity scale ranging from 0 (absent) to 3 (discontinuation of therapy, additional therapy, or both required).

Quality of life

Three validated quality of life questionnaires, one used in pediatric patients with asthma, one used in adult patients treated with amlodipine for hypertension, and SF-36, were adapted for use in this study [15–17]. The questionnaire consisted of 52 global and specific questions about psychological well-being, health perception, and physical ability. Questionnaires were completed at the time of enrollment into the study and at the end of the study.

Compliance

Compliance of amlodipine was measured by pill count, pharmacy records, and telephone interviews.

Statistics

Statistical power was used to determine the number of patients required to detect a statistical difference before and after amlodipine treatment. Mean systolic and diastolic BP obtained from HBP and ABPM were compared between baseline and stabilized BP of the latest measurements using Students paired *t*-test and correlation coefficient. The Cronbach's alpha test of reliability was used to test the reliability of the quality of life questionnaire. Responses to quality of life questions before and after amlodipine treatment were then compared using the Wilcoxon signed rank nonparametric test.

Results

Twenty-one (10 male, 11 female; 1 Asian, 3 African Americans, and 17 Caucasians) with a mean age of 13.1±3.6 years (range 6–17 years) participated in the study (1-β=0.9) (Table 1). Four patients had been on monotherapy [clonidine (1), isradipine (1), enalapril (1), nifedipine sustained release (1)] and 2 had been on combination therapy [enalapril+hydrochlorothiazide (1), enalapril+nifedipine sustained release (1)]. Five patients (23.8%) had renal causes of hypertension and 16 patients (76.2%) were diagnosed with essential hypertension. The causes of renal hypertension included proliferative glomerular nephritis (1), renal scarring secondary to recurrent urinary tract infections (1), renal transplant (1), and chronic pyelonephritis (2).

Fourteen patients were newly diagnosed with hypertension and 7 patients were either poorly controlled on existing antihypertensive agents (3) or had adverse effects to other antihypertensive agents (4). Six patients had concomitant conditions, including mild to moderate asthma (2), attention deficit disorder (1), mild to moderate asthma and mild gastroesophageal reflux disorder (1), mild gastroesophageal reflux disorder (1), and Tourette syndrome along with attention deficit disorder, depression, and obessive-compulsive disorder (1).

Nineteen patients (90.5%) completed the study and 2 withdrew (9.5%) before completion of study. Attainment of goal BP based on the 95th percentile for age and gender measured by both the average HBP and repeat ABPM at the highest amlodipine dose obtained was reached in 15 of 20 patients that were remonitored. Of 5 patients that did not achieve their goal BP on amlodipine alone, 4 had renal causes of hypertension. Three patients required two or more antihypertensive agents and the fourth renal patient withdrew before BP stabilization. The nonrenal patient, who had poorly controlled BP initially on enalapril and nifedipine sustained release, was switched to enalapril and amlodipine. This patient demonstrated BP normalization only on triple antihypertensive therapy (atenolol, enlaparil, and amlodipine).

Amlodipine alone was effective in 14 patients [renal (2) and essential (12)], and more than one antihypertensive agent was required to treat 7 patients [renal (4), essential (3)]. The mean initial dose of amlodipine was 0.07±0.04 mg/kg per day. The mean time for stabilization of BP for all patients was 44.2±29.6 days based on home monitoring and 79.2±45.2 days based on ABPM. The maximum dose of amlodipine used to control BP for both monotherapy and polytherapy antihypertensive regimens was age dependent. The mean dose for all children <13 years (0.29±0.11 mg/kg per day) was nearly two times higher than that required for children ≥13 years (0.16±0.11 mg/kg per day) ($t_{df=19}$ =3.17, P=0.005). The mean dose for both essential (0.23±0.14 mg/kg per day) and renal (0.24±0.13 mg/kg per day) causes of hypertension were similar ($t_{df=19}$ =0.35, P=0.08). Additionally, the dose of amlodipine for 4 obese patients in the ≥13 years group, defined as >20% of their ideal body weight, was determined using their body surface index (0.13±0.09 mg/kg per day) and compared with their corresponding actual body weight dose (0.19±0.14 mg/kg per day). The obese patients, on average, required a higher dose if actual body weight was used, but no significant difference in dose was found using either method (P=0.36). The mean 95th percentile BP goal for all patients was compared with the mean ABPM value at the highest amlodipine dose obtained (Table 2). Patients with essential hypertension obtained their goal systolic (P<0.01) and diastolic (P<0.01) BP. As a group, the patients with renal causes of hypertension attained their diastolic BP goal; however, their systolic BP exceeded the 95th percentile goal.

During the course of the study, baseline and follow-up laboratory tests were performed. The mean baseline and follow-up fasting total cholesterol concentrations were 177.0±54.1 and 186.8±71.3 mg/dl respectively (P=0.34), and mean baseline and follow-up fasting triglyceride concentrations were 120.1±78.3 and 129.4±72.9 mg/dl, respectively (P=0.46). One renal transplant patient was noted to have increased CSA plasma concentrations on amlodipine. On isradipine 5 mg twice daily, the plasma CSA concentration on 200 mg/day of CSA was approximately 247 ng/ml; on amlodipine 2.5 mg daily, the CSA concentration was 366 ng/ml at the same dose of CSA. The dose of CSA was subsequently reduced, with a decrease in CSA plasma concentration to 224 ng/ml. For all patients, the laboratory abnormalities were minor and/or not considered to be related to amlodipine treatment. No patients withdrew from amlodipine therapy based on laboratory findings.

Ten patients had adverse effects while receiving amlodipine. Seven patients experience three or more adverse effects, while the remaining 3 patients experienced one

Table 1 Patient demographics and pre and post amlodipine (AML) blood pressures (BP)

Patient no.	Gender	Ethnicity	Age (years)	Diagnosis of hypertension	Baseline office BP (mm Hg)	Baseline ABPM (mm Hg)	AML maintenance dose (mg/kg per day)	Final home BP (mm Hg)	Final ABPM (mm Hg)
1	M	C	8.7	Ess	131±10 81±8	139±11 86±9	0.50	113±12 77±14	102±8 59±9
2	F	AA	6.0	Ess	124±2 67±9	121±13 72±15	0.33	109±16 69±1	106±15 64±15
3	M	C	17.9	Ess	152±0 94±0	125±13 70±13	0.085	125±16 74±7	129±9 70±9
4	M	C	16.7	Ess	130±6 87±1	127±10 69±10	0.08	131±10 81±8	123±13 66±10
5	M	C	16.9	Ess	146±11 100±0	156±18 78±15	0.22	136±7 75±6	131±14 68±12
6	M	C	10.2	Ess	116±0 85±1	129±13 83±14	0.42	119±3 73±3	113±9 68±12
7	M	C	15.9	Ess	148±0 100±0	128±12 74±10	0.29	127±8 81±7	121±11 72±9
8	F	C	12.6	Renal	134±0 84±0	149±10 90±10	0.34	134±10 79±10	118±11 62±14
9	M	C	15.3	Ess	148±25 91±10	143±13 80±16	0.02	W	W
10	F	C	10.0	Ess	119±6 74±10	119±12 71±11	0.16	111±13 82±11	132±12 82±14
11	M	C	16.8	Ess	147±15 72±0	130±16 62±17	0.29	129±13 77±10	129±14 59±11
12	M	A	13.8	Ess	155±6 85±9	126±12 69±11	0.10	118±7 69±5	125±8 65±9
13	F	C	8.7	Renal	119±1 73±4	125±13 71±15	0.39	117±5 77±6	122±14 65±14
14	F	AA	15.8	Ess	145±10 85±4	137±10 84±10	0.16	114±9 63±4	127±13 76±12
15	F	C	13.9	Ess	136±5 78±14	128±18 75±17	0.05	115±16 84±15	123±16 65±15
16	F	AA	12.2	Ess	164±6 98±0	124±12 70±16	0.28	115±9 67±22	124±11 65±15
17	F	C	15.8	Ess	137±11 75±6	129±12 73±13	0.12	114±10 75±13	121±9 71±8
18	F	C	7.7	Renal	145±0 94±0	119±11 73±10	W	W	W
19	M	C	13.8	Ess	140±3 93±4	131±12 75±19	0.37	128±4 62±15	127±14 64±12
20	F	C	9.2	Renal	120±10 79±11	130±13 82±12	0.19	120±5 77±12	104±10 59±7
21	F	C	16.4	Renal	121.50±1 73.50±11	119±12 71±15	0.045	123±8 83±11	121±9 70±10

ABPM, 24-h Ambulatory monitor; C, Caucasian; AA, African American; A, Asian; W, withdrew from the study; Ess, essential hypertension

or two adverse effects. Twenty-three mild adverse effects were reported. Six patients reported fatigue, which resolved in 4 patients when BP control was achieved. Five patients experienced headaches at lower doses of amlodipine during the titration phase of the study, which resolved after BP was controlled. Dizziness upon exercise occurred in 2 patients, abdominal pain in 3, facial flushing in 4, peripheral edema in 1, and nausea in 1. Vomiting occurred in 1 transiently upon dosage change and resolved without intervention.

Six severe adverse effects were reported. Two patients experienced peripheral edema. One patient required the addition of furosemide, and the use of amlodipine was halved in another with resolution of symptoms. The sec-

Table 2 Comparison of mean 95th percentile BP and mean post ABPM BP at final AML dose

Measured parameter	Mean 95th percentile BP goal (SD)	Mean post ABPM BP final AML dose (SD)	Correlation factor (*r*)	*t* value	*P*
Overall BP systolic (mm Hg) (*n*=20)	126.7±8.09	123.95±10.54	0.39	1.17	0.25
Overall BP diastolic (mm Hg) (*n*=20)	82.00±4.94	69.32±6.36	0.07	7.10	0.01
Essential BP systolic (mm Hg) (*n*=15)	128.53±7.61	122.20±8.79	0.75	4.18	0.01
Essential BP diastolic (mm Hg) (*n*=15)	83.29±4.27	67.29±5.04	0.43	11.95	0.01
Renal BP systolic (mm Hg) (*n*=5)	121.20±7.56	129.20±14.53	0.27	1.24	0.28
Renal BP diastolic (mm Hg) (*n*=5)	78.40±5.37	75.00±6.67	0.39	1.13	0.32

Table 3 Comparison of pre and post-AML treatment outcome measures [a, b]

Measure	*n*	Pre treatment	Post treatment
Overall health	20	29.60±6.72	+32.30±6.60 **
Health outlook	20	9.55±4.20	+ 8.65±4.18
Activity level	20	28.60±2.54	+29.10±2.34 *
Social functioning	20	3.95±1.05	+ 4.35±0.93 *
Psychological well-being	20	26.45±8.48	+24.25±7.89

[a] Values are expressed as means±SD
* $P<0.05$, ** $P<0.01$
[b] Improvement is indicated by a positive change

ond patient experienced chest pains, moderate peripheral edema, and dizziness 2 days after ranitidine was initiated, and the dose of amlodipine was halved with resolution of symptoms. Another patient experienced chest pains after 2 days on amlodipine at a dose of 0.05 mg/kg per day. The drug was withdrawn and reintroduced without further incidence at a dose of 0.02 mg/kg per day. The patient later discontinued amlodipine without additional antihypertensive management.

Patients completed all sections of the quality of life questionnaires except for 7.3% of questions. The questionnaire was determined to be internally consistent with an alpha value of 0.89. Comparison between baseline and stabilization or maximum dose of amlodipine attained demonstrated significantly improved scores for overall health ($P<0.01$), activity level ($P<0.05$), and social functioning ($P<0.05$) (Table 3).

Thirteen patients (61.9%) achieved full compliance by taking amlodipine once daily as prescribed. Compliance checks revealed missed doses ranging from 1 to 3 (mean 0.57±0.87) per month. One patient missed 3 doses per month; one missed 2 doses per month, and five missed 1 dose per month.

Discussion

In this study, the ABPM was used to monitor the efficacy of amlodipine as a once daily antihypertensive agent in 21 pediatric patients with hypertension. ABPM has been validated as effective for evaluating antihypertensive therapy in adults [18–20].Thirteen patients with mild to moderate essential hypertension attained a BP less than or equal to the 95th percentile based on age and gender on amlodipine alone, according to the guidelines of the Second Task Force on BP Control in Children [21]. Two patients with moderate essential hypertension required additional antihypertensive agents to attain their BP goal. Patients with essential hypertension two were <13 years required twice the amount of amlodipine compared with those ≥13 years to achieve their goal BP. This observation may reflect an increased metabolism of amlodipine in younger patients, which has been observed with other medications [22]. Similar amlodipine dosage requirements were seen with the renal patients based on age. Complete BP control in the 5 patients with renal causes of hypertension, however, was achieved with amlodipine monotherapy in only 1 patient. In contrast to this study, Khattak et al. [14] did not observe an age-dependent dose requirement in the 15 hypertensive pediatric patients retrospectively studied. This discrepancy is likely related to the fact that only 27% of the patients >13 years obtained a BP of less than or equal to the 95th percentile based on age and gender at the maximum daily dose of amlodipine tried.

No correlation was seen between baseline office and ABPM or HBP and ABPM measurements performed at stabilized amlodipine doses. Baseline systolic BP was higher in 29% of patients measured by ABPM compared with BP measured at the office. Stabilized systolic BP measured by ABPM were also higher than 42% of the BP readings measured at home (Table 1). The difference between the three methods is probably not the result of the technique used by the ABPM to obtain systolic and diastolic measurements, but related to the timing of BP measurements, such as the "white coat effect" and/or the activity level of the child [21, 23–25]. HBP monitoring is an inexpensive method to follow a patient's response to an antihypertensive agent. Nonetheless, ABPM is a useful tool to determine if BP stabilization has been achieved by therapeutic intervention based on HBP monitoring, and to confirm the diagnosis of hypertension in pediatric patients with clinically elevated BP [26, 27].

Amlodipine was well tolerated by most children. No patients withdrew from the study based on adverse effects experienced. The types of reported adverse effects were similar to those detected in other amlodipine studies [14, 28]. The incidence of adverse effects, however, was higher in this study. This has been reported with other medications in pediatric patients and may be related to the pharmacokinetics of medications in this population [22, 29]. Mild abdominal distress in 4 patients occurred upon initiation of amlodipine, but resolved with continued use. Headache and fatigue, the most commonly reported adverse effects, resolved with time when the child became normotensive on a consistent dose of amlodipine or antihypertensive combination.

Osterloh [28] showed that headache occurred at the same rate as the placebo group in 2,988 adult patients. Fatigue, however, occurred at a higher rate in the amlodipine-treated group (4.6%) than the placebo group (2.9%) ($P<0.05$). In this large study, patients treated with amlodipine complained of fatigue more often than those treated with hydrochlorothiazide, verapamil, and diltiazem, but less often than those on beta-blockers. Peripheral edema, dizziness, facial flushing, and fainting appeared to be dose-related phenomena and related to a reduction in peripheral resistance. In a double-blind, dose response study in adults, patients who received 10 mg of amlodipine daily experienced 1.5 times more peripheral edema and flushing than those patients who received lower doses [28]. The peripheral edema experienced by our patients resolved with either the addition of hydrochlorothiazide or a reduction in the dose of amlodipine. Chest pains occurred in 2 patients and lasted 1–2 h. In both cases, the dose of amlodipine was reduced without further incidence.

The renal transplant patient described demonstrated a 47% increase in CSA plasma concentration on the same dose of CSA after isradipine 5 mg twice daily was replaced by amlodipine 2.5 mg daily. The maintenance dose of CSA was reduced in half to achieve a therapeutic plasma concentration. Reports of amlodipine interaction with CSA are inconsistent. No clinically significant difference in the AUC, t_{max} , and C_{max} of CSA was observed in ten renal transplant patients with hypertension who received amlodipine 5 mg daily [12]. Pesavento et al. [13] however, showed that CSA plasma concentrations increased on average 40% ($P=0.003$) in 11 hypertensive renal transplant patients. Health care providers need to be aware of the potential of drug-drug interactions and monitor CSA plasma concentrations accordingly.

No unfavorable changes in total cholesterol and triglycerides were observed. Ahaneku et al. [30] noted no significant change in lipids and lipoprotein concentrations between baseline and patients treated with amlodipine 5 mg or 10 mg daily for 12 weeks. There was a slight decrease in low-density lipoprotein-cholesterol, however, from 165±17 mg/dl at baseline to 133±12 mg/l on amlodipine 2.5–10 mg daily for 4 weeks. Other calcium antagonists have rarely been shown to significantly influence serum cholesterol and serum triglyceride concentrations, unlike other antihypertensive medications such as thiazide-type diuretics, beta-blockers, and alpha-blockers [31–33].

We focused our analysis of quality of life at baseline and at the time of blood pressure stabilization based on the ABPM. A statistically significant improvement in current overall health was observed over the average treatment period of 79.2±45.2 days. This finding corresponded to a trend in improvement in future health outlook. Activity level, including vigorous and moderate activities, slightly improved on amlodipine. Only a small but significant change was noted, but few patients were limited in their activities at baseline. A slight improvement compared with baseline was observed in the patient's ability to interact socially with their friends, classmates, and relatives. This observation corresponded to a positive trend in psychological well-being, involving attitude, energy level, and emotional state. Improvement or no change in quality of life was observed in all indices examined.

Compliance in this study was based on the physical act of administering amlodipine, and the associated adverse events the patients experienced. In the case of the former, a trend toward improvement was seen. Of the 3 patients who were noncompliant with their antihypertensive medications in the past, all 3 remembered to take their medications during this study. This observation is likely related to the ease of remembering to administer a medication once daily versus twice daily, bi-weekly phone calls, and/or the patient's perceived demand to perform [34]. Compliance based on adverse effects experienced produced mixed results. Of the 10 patients who experienced adverse events with amlodipine, 4 were noncompliant, and 2 of these 4 patients also experienced severe adverse events of fainting and edema. A direct relationship between medication compliance and adverse events has also been noted with other hypertension studies [16, 35].

In summary, amlodipine is an effective once daily antihypertensive agent with an acceptable safety profile and effect on quality of life for pediatric patients. Higher doses of amlodipine are required for pediatric patients ≥12 years. Amlodipine can be used once daily as mono-

therapy for pediatric patients ≥12 years with essential hypertension. Large, crossover studies of amlodipine compared with other calcium channel antagonists and angiotensin converting enzyme inhibitors are needed to further evaluate the safety and efficacy of this antihypertensive agent in the pediatric population.

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