THE EFFICACY AND SAFETY OF AMLODIPINE IN PEDIATRIC PATIENTS

by

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A thesis submitted in conformity with the requirements for the degree of Master of Science
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Master of Science 1997
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ABSTRACT:

In order to determine the efficacy and safety of amlodipine in children three clinical studies were conducted. The first study (retrospective) performed on 23 pediatric transplant and nephrology patients showed that an antihypertensive regimen with amlodipine had both significantly lower systolic (p<0.05) and diastolic (p<0.05) blood pressure than baseline therapy. A second retrospective study on 15 pediatric bone marrow transplant patients confirmed the results of the first study. A prospective study in eleven pediatric renal transplant patients demonstrated that no significant difference existed between amlodipine and nifedipine/felodipine in terms of mean 30-day blood pressure (systolic: p=0.09; diastolic: p=0.27), mean day time blood pressure (systolic: p=0.78; diastolic: p=0.65), mean nighttime blood pressure (systolic: p=0.96; diastolic: p=0.95), and mean patient compliance (p=0.94). Amlodipine was generally well tolerated in all three studies. Thus, amlodipine is safe and provides comparatively effective blood pressure control in children. This drug has unique clinical value in children due to once-daily dosing as a liquid preparation.
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1. INTRODUCTION:

**PEDIATRIC HYPERTENSION**

The incidence of pediatric hypertension has been estimated at 1 to 3% in children under 13 years of age\(^1\). Although its incidence in children is significantly lower than in adults, hypertension is not rare in childhood and its detection and subsequent control is a major concern in health care\(^2\).

**Task Force on Blood Pressure Control in Children**

Up until the late 1970s, very little data pertaining to pediatric hypertension was available because no consensus existed on a proper definition of hypertension in children and there was an absence of standardized approaches in place for evaluation of this disease. In order to address these issues, the Task Force on Blood Pressure Control in Children was created by the National Heart, Lung, and Blood Institute in the United States in 1977.

A report was released by this task force in 1977 which consisted of sex- and age-specific normalized blood pressure distribution curves in children that had been derived from blood pressure data collected from numerous epidemiologic studies. In this report hypertension was defined as blood pressure values above the 95th percentile for a given age and gender\(^2,3\).
Second Task Force on Blood Pressure Control in Children

As more national data on blood pressure in children were collected in the following decade, a second task force was created to re-examine the issue of hypertension in this cohort. The task force’s subsequent 1987 report compiled normative blood pressure data on over 70,000 children and included minority groups for the first time (e.g. African-Americans). Percentiles specific for age and sex were established and are currently considered the standard tool for the interpretation of blood pressure in children. Today, hypertension in a given child is defined as three accurate measurements taken on three separate occasions that exceed the 95th percentile for age and sex.

Since blood pressure increases with not only age, but also weight and height during childhood, assessment of hypertension in childhood may be complicated by the differential growth rate of children. A reanalysis of the available blood pressure data by Rosner et al. used gender and age as well as height to classify blood pressure. The use of a child’s height percentile (derived from the standard growth curve) prevents the false conclusion that very tall children are hypertensive when they are normotensive, and that very short children have normal blood pressure when they are in fact hypertensive. Thus, height age, rather than chronological age is thought by some researchers...
to be a more superior determinate of blood pressure during adolescence, a period when there are significant variations in growth\textsuperscript{2,6}.

**Etiology of Childhood Hypertension**

The underlying causes of hypertension differ substantially between the pediatric and adult populations. For example, primary or essential hypertension accounts for over 90\% of hypertension in adults but is rare in early childhood, although its incidence increases with age in children\textsuperscript{7,8}.

In contrast, secondary causes of hypertension are responsible for approximately 90\% of hypertension in children under 10 years of age. The majority of cases of secondary hypertension can be attributed to renal parenchymal disease in children\textsuperscript{9}. To a lesser extent, disorders of the renovascular, cardiovascular, and endocrine systems as well as drug-induced causes have been implicated as underlying causes of pediatric hypertension\textsuperscript{10-13}. The most difficult type of hypertension to treat is that associated with chronic renal failure\textsuperscript{1}. 


DRUG-INDUCED CAUSES OF POST TRANSPLANTATION

HYPERTENSION

Two of the most commonly used immunosuppressant agents, cyclosporine and corticosteroids, are known to induce hypertension in transplant patients\textsuperscript{14}. Cyclosporine was introduced in 1984 and was soon thereafter, widely used to treat many solid organ and bone marrow transplant patients since it increased allograft survival without appearing to cause suppression of the bone marrow and it did not increase the incidence of opportunistic infections in treated individuals\textsuperscript{15,16}. For example, in the early 1980’s a clinical trial demonstrated that the graft survival rate after renal transplantation improved by approximately 10\% following the introduction of cyclosporine\textsuperscript{17}.

Adverse Effects of Cyclosporine

Unfortunately, nephrotoxicity and hypertension\textsuperscript{18} are major adverse effects of cyclosporine administration in patients who have received renal\textsuperscript{19,20}, bone marrow\textsuperscript{21,22}, hepatic\textsuperscript{23}, and cardiac\textsuperscript{24} transplants. For instance, Kone et al.\textsuperscript{25} demonstrated that 64\% of bone marrow transplant patients studied (n=64) developed acute renal failure following cyclosporine administration and the
incidence of systemic hypertension was approximately 75%. Both adverse events typically developed within one month of the initiation of cyclosporine therapy.

**Incidence of Hypertension in Transplant Patients Following Cyclosporine Administration**

Various studies\(^{26-33}\) in adults have demonstrated that the incidence of hypertension following renal transplantation increased from a range of 45\%-55\% to one of 67\%-86\% following the use of cyclosporine. In contrast to renal transplant patients, only a small percentage of adults (5\%-10\%) who received a bone marrow transplant were hypertensive prior to the routine use of cyclosporine\(^{18,21,27,34-36}\). One study found an incidence of hypertension in bone marrow transplant patients (n=47) of approximately 50\% following cyclosporine therapy. This incidence of hypertension increased to 70\% in patients who also received corticosteroids\(^{35}\). Thus, it appears, for the most part, that post transplantation hypertension in bone marrow transplant patients is drug-induced. This is not always the case following renal transplantation.
Causes of Post Transplantation Hypertension

in Renal Transplant Patients

Hypertension following renal transplantation is usually multifactorial in nature and, as a result, is poorly understood since it is difficult to delineate the contribution of different factors that are responsible for the disease in a given patient. Both intrinsic and extrinsic causes of hypertension have been identified.

Intrinsic causes of hypertension are usually those that result from direct damage to the renal allograft and include acute and chronic rejection and the recurrence of the original renal disease state (e.g., focal glomerulosclerosis) which necessitated transplantation\textsuperscript{37}. Chronic rejection is the most common cause of chronic post transplantation hypertension in renal transplant patients\textsuperscript{38}.

Post transplantation hypertension caused by renal artery stenosis, drugs, and the presence of a patient’s native kidneys are external causes of this disease since they do not directly damage the renal allograft. Native kidney-induced hypertension is a specialized type of post-transplantation hypertension. Studies have demonstrated that there was a greater prevalence of hypertension in patients whose own kidneys were not removed prior to transplantation compared to those who had a nephrectomy before receiving their transplants\textsuperscript{37,39,40}. Further evidence showed hypertension improved or subsided.
when the native kidneys were later removed following transplantation\textsuperscript{41,42}. Hypertension induced by renal artery stenosis and native kidneys is commonly corrected through surgical or radiological techniques.

**Long-term Health Concerns Associated With Post Transplantation Hypertension**

Hypertension following renal transplantation is considered a serious long-term health issue that concerns transplant physicians since this condition is associated with a significant decrease in graft survival\textsuperscript{43-45}. Furthermore, cardiovascular disorders remain the most significant cause of death in renal transplant patients and hypertension is postulated to be the most important risk factor for cardiovascular morbidity and mortality in this population\textsuperscript{46,47}. For instance, hypertension was found to be a major risk factor for atherosclerosis in adult renal transplant patients and it has a negative effect on a patient’s survival and rehabilitation\textsuperscript{48}. Physicians who treat children with renal transplants should be concerned with the findings discussed above since pediatric patients appear to have a greater incidence of post transplantation hypertension than adults\textsuperscript{49}.
Pharmacological Treatment of Post Transplantation Hypertension

The introduction of cyclosporine has changed the nature of post-transplantation hypertension and has led to considerable changes in the pharmacological treatment of this condition. Prior to the introduction of cyclosporine, the renin-angiotensin system appeared to play a major role in most types of post-transplantation hypertension, but is thought now to play only a minor role. Several clinical studies during the cyclosporine era have suggested that the circulating renin-angiotensin system is suppressed in posttransplantation hypertension, even in the presence of sodium restriction. In fact, the use of angiotensin-converting enzyme (ACE) inhibitors as monotherapy for posttransplant hypertension has resulted in minimal antihypertensive efficacy. However, the combination of enalapril maleate and a diuretic has been shown to be effective as treatment for post-transplantation hypertension in heart transplant patients.

Since cyclosporine can induce hyperkalemia and acidosis by partially inhibiting the renal secretion of potassium and hydrogen ions, ACE inhibitors must be used with caution since they may aggravate hyperkalemia and acidosis. Moreover, cyclosporine administration causes significant increases in uric acid levels, so the use of diuretic therapy is often not encouraged to treat transplant patients since this may worsen the hyperuricemia.
Mechanisms of Cyclosporine-induced Hypertension

The primary mechanism by which cyclosporine is believed to cause acute nephrotoxicity is through vasoconstriction of the afferent arteriole of the glomeruli\textsuperscript{57}. This vasoconstrictive mechanism is also thought by many to induce systemic hypertension through decreased effective renal blood flow (ERBF) which leads to a decrease in the glomerular filtration rate (GFR) and an increase in intravascular volume via sodium retention\textsuperscript{58,59}.

However, cyclosporine is also thought by some investigators to cause post transplantation hypertension through a primary mechanism involving adrenergic-mediated vasoconstriction\textsuperscript{60,61}. It has been demonstrated in experimental studies that renal nerves may play an important role in alterations in both renal blood flow and sodium homeostasis following cyclosporine administration. It was further shown that these effects were reversed or prevented following denervation of the kidney or by adrenergic blockade\textsuperscript{35,62,63}. However, these results have been questioned since it was demonstrated clinically that renal transplant patients who were functionally denervated still exhibited cyclosporine-induced vasoconstriction and post-transplantation hypertension\textsuperscript{64}.

Recent studies have demonstrated that calcium channel blockers can partially reverse the vasoconstrictive effects of cyclosporine which makes
them an ideal class of antihypertensive drugs for first-line treatment in posttransplantation hypertension\textsuperscript{65-70}.

Before further discussing the benefits of using calcium channel blockers for the treatment of cyclosporine-induced post-transplantation hypertension, the properties of this class of antihypertensive will be discussed.

**CALCIUM CHANNELS**

Calcium channels are ion-selective pores that are formed from membrane-spanning proteins of cells in muscle and heart, which selectively admit Ca\textsuperscript{2+} ions\textsuperscript{71}. Calcium channels are divided into two subgroups based on their location and principal function: the calcium release channels of the sarcoplasmic reticulum and the voltage-activated, transsarcolemmal channels. The first channel subtype allows Ca\textsuperscript{2+} ions to move from storage loci in the sarcoplasmic reticulum to the cytosol where these ions initiate contraction. The latter channel subtype facilitates the voltage-dependent inward flux of Ca\textsuperscript{2+} ions across a normally impermeable cell membrane\textsuperscript{72}.

The voltage-dependent calcium channels are present in most cells but are not found in red blood cells or platelets\textsuperscript{73}. This channel subtype is further subdivided into L, T, N, and P-type voltage-activated Ca\textsuperscript{2+} channels based on
their differing biophysical properties and sensitivity to specific chemicals and toxins\textsuperscript{74,75}.

All commercially available calcium channel blockers only affect the function of L-type Ca\textsuperscript{2+} channels although there is a novel type of pharmaceutical agent (mibefradil) being clinically tested that causes selective blockade of the T-type (transient, low voltage) calcium channel\textsuperscript{76}. L-type calcium channels are unique in that they possess large ion conductance, remain open for relatively long periods of time, and are inactivated at a relatively slow rate. L-type channels are localized in skeletal, cardiac, and vascular muscle and play a primary role in muscle contraction\textsuperscript{71}.

**Structure of the L-type Ca\textsuperscript{2+} Channel**

The L-type channel is an oligomeric structure that is composed of five subunits ($\alpha_1, \alpha_2, \beta, \gamma,$ and $\delta$) and is assembled in the sarcolemma with the $\alpha_1$ subunit providing the channel's functional central pore\textsuperscript{77,78} (refer to figure 1, page 13).

The $\alpha_1$ subunit (refer to figure 2, page 14) is comprised of 1873 amino acids and consists of four repeating transmembrane motifs denoted I, II, III, and IV\textsuperscript{79}. Each motif is made up of six segments (denoted S) and each segment is connected to another by extracellular loops. Segments 2 and 3, and 4 and 5
of each motif and segments 6 and 1 of motifs I and II, of II and III, and III and IV are connected to intracellular loops\textsuperscript{72}. The fourth segment (S4) of each of the 4 repeating motifs (S4) is postulated to form a component of the voltage-sensing mechanism of the ionophore, because it contains charged amino acid residues at every third or fourth position\textsuperscript{77}.

The $\alpha_2$ and $\delta$ subunits are two proteins linked by disulphide bonds and are encoded by the same gene. The function of these subunits is not known although it has been suggested that the $\delta$ subunit acts as a membrane anchor for the $\alpha_2$ protein\textsuperscript{80}. In addition, it has also been postulated that the $\alpha_2/\delta$ complex may modulate the ability of the $\alpha_1$-subunit to conduct Ca\textsuperscript{2+} ions and bind calcium channel blockers\textsuperscript{81}.

The $\beta$-subunit has been clearly shown experimentally to enhance the ability of the $\alpha_1$-subunit to conduct calcium ions\textsuperscript{82}. The functional importance of the $\gamma$ subunit has not been elucidated\textsuperscript{74}.
FIGURE 1: SUBUNIT COMPONENTS OF THE L-TYPE CALCIUM CHANNEL

β
α
γ
α
Calcium Ions
FIGURE 3: STRUCTURAL COMPONENTS OF THE ALPHA SUBUNIT OF THE L-TYPE CALCIUM CHANNEL
Location of Calcium Channel Blocker Binding Sites in the Alpha$_1$-Subunit

The chemical structure of calcium channel blockers consists of those which are dihydropyridine-based (e.g. nifedipine, felodipine, amlodipine) or phenylalkylamine-based (e.g. verapamil) and those which are derived from benzthiazepines (e.g. diltiazem). The binding of dihydropyridine-based calcium channel blockers to the alpha$_1$-subunit differs primarily from that of the other two classes of calcium channel blockers in that their binding sites are located on the extracellular side of the cell membrane, as opposed to intracellularly$^{83}$.

It is postulated that the dihydropyridine-based calcium channel blockers may bind to three distinct high affinity binding site regions of the alpha$_1$ subunit. These binding sites include amino acid residues located within transmembrane segment 6 of both motifs III and IV and the extracellular loop of segments 5 and 6 of motif III$^{84-86}$.

Mechanism of Action of Calcium Channel Blockers

All three subclasses of calcium channel blockers have similar mechanisms of action but have differ with respect to their pharmacokinetic profile, adverse effects, and myocardial and vascular selectivity$^{87}$. Calcium
channel blockers inhibit the transmembrane influx of calcium ions into vascular and cardiac muscle cells which results in vasodilation and a reduction in peripheral vascular resistance$^{88}$.

**First and Second Generation Calcium Channel Blockers**

Calcium channel blockers are referred to as first or second generation drugs. First-generation calcium channel blockers were the earliest form of these type of antihypertensives developed for clinical use and include the prototype compounds verapamil, diltiazem, and nifedipine. The second generation calcium channel blockers were developed to overcome some of the limitations inherent in their first-generation prototypes.

The limitations of the first-generation calcium channel blockers include their:

1. relatively short duration of action
2. poor bioavailability when administered orally
3. lack of tissue selectivity
4. high frequency of unacceptable side-effects
5. wide variations in peak-to-trough plasma concentrations during the dosage interval$^{89}$
**AMLODIPINE**

Amlodipine is a relatively new, second-generation dihydropyridine-based calcium channel-blocker. Other common examples of second generation dihydropyridine calcium-channel blockers include felodipine, isradipine, nicardipine, nimodipine, nisoldipine, and nitrendipine. The rationale for synthesizing amlodipine was to create a drug with a longer half-life and improved bioavailability than its prototype, nifedipine\(^9^0\). However, it has become more evident that amlodipine has many other advantages over both first and second generation calcium channel blockers.

**Chemistry**

Amlodipine has unique physiochemical properties that set it apart from all other dihydropyridine-based calcium channel blockers (figure 3, page 18). The drug possesses a side chain in the 2-position of the dihydropyridine ring which contains a terminal basic amino group (pK\(_a\) =8.6). As a result, amlodipine is 94% ionized at physiological pH. This high degree of ionization is one identifiable factor which may account for the water solubility of this agent. All other dihydropyridines in clinical use have pK\(_a\) values below 3.0 and are neutral under these conditions, and are not water soluble\(^9^1\).
FIGURE 3: COMMON CHEMICAL STRUCTURES OF DIHYDROPYRIDINE-BASED CALCIUM CHANNEL BLOCKERS
**Unique Binding Profile**

Amlodipine also binds to the α₁-subunit of the calcium channel complex in a unique manner since its specific binding can be inhibited by not only calcium channel blockers of the dihydropyridine class, but also by phenylalkylamine-based and benzothiazepine-based calcium channel blockers. It is postulated that amlodipine binds to the three major types of calcium channel blocker binding sites but its primary site of action is located within the dihydropyridine binding domain of the calcium channel 92-95.

**Vascular Selectivity**

Amlodipine is more vascular selective than its prototype nifedipine and other first-generation calcium channel blockers. The selectivity factor (relative effect on the vasculature versus that on the myocardium) of amlodipine is 8096-97 and it is 2098 for nifedipine. In addition, the negative inotropic effect of nifedipine is approximately five times that of amlodipine96. Calcium channel blockers with less negative inotropy are preferred by physicians because there is less chance of cardiac failure in patients, particularly in those with impaired left ventricular function99.
**Long Duration of Action**

Much of the long duration of amlodipine results from its unique pharmacokinetic profile. First, amlodipine possesses a longer duration of action when compared to other calcium channel blockers, which permits once daily dosing for 24-hour control of hypertension\textsuperscript{100-102}. The intrinsic plasma elimination half-life of a single dose of amlodipine in adults is 36 hours, but increases up to 45 hours following repeated dosing. Steady state plasma concentrations of amlodipine are reached approximately 7 days after once-daily repeated dosing\textsuperscript{103}. In contrast, short-acting nifedipine has an elimination half-life of only 2 hours so that multiple daily dosing is required\textsuperscript{104}.

Some factors responsible for the relatively long intrinsic elimination half-life of amlodipine include its relatively slow rate of hepatic metabolism\textsuperscript{105} and unusually large volume of distribution (21 L/kg)\textsuperscript{106}. One advantage of possessing a long half-life is that it ensures there will be minimal fluctuations in peak-to-trough plasma concentrations during a given amlodipine dosage interval. Amlodipine has a relatively low peak-to-trough plasma concentration of 1.5,\textsuperscript{103} which is even substantially smaller than the values found in slow-release formulations of other calcium channel blockers (e.g. felodipine ER, 2.9; nifedipine SR, 10.4)\textsuperscript{107,108}.

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Bioavailability

Because amlodipine does not undergo extensive first-pass metabolism and is completely absorbed from the gastrointestinal tract, it has the advantage of possessing a relatively high bioavailability (80% in hypertensive adults)\textsuperscript{109}. Many of the other calcium-channel blockers undergo extensive first-pass metabolism and, as a result, have low bioavailability percentages (e.g. felodipine ER, 22\%\textsuperscript{110}, nifedipine, 43\%\textsuperscript{104}). Drugs with a low bioavailability (e.g. felodipine ER) tend to exhibit a high degree of inter- and intrapatient variability in terms of their pharmacokinetic profile and efficacy, and both parameters can be profoundly altered by foods\textsuperscript{111}, fluids (e.g. grapefruit juice\textsuperscript{112}, alcohol\textsuperscript{113}), and other drugs (e.g. digoxin\textsuperscript{114}, cimetidine\textsuperscript{115}).

Onset and Offset of Action

When administered orally, amlodipine is absorbed completely and relatively slowly with peak levels occurring at between 6 and 12 hours after dosing\textsuperscript{103}. The majority of the other second-generation dihydropyridine-based calcium channel blockers take from 1 to 2 hours to reach peak plasma levels after oral administration\textsuperscript{116-120} with the exception of felodipine ER, which may take up to 8 hours in some individuals\textsuperscript{110}. In addition to the slow rate of absorption of amlodipine, the slow onset of action is also thought to result
from its relatively long hepatic transfer time and its slow rate of association of this blocker to the calcium channel. Similarly, the relatively slow offset of action is presumably due to the slow rate of dissociation of amlodipine from the calcium channel. 

**Adverse Effect Profile of Amlodipine**

Because calcium channel blockers act through a mechanism involving vasodilation, the predominant adverse effects commonly associated with these drugs are extensions of their pharmacological action and include peripheral edema, headaches, facial flushing, and dizziness. Amlodipine has a low incidence of these adverse effects and this is not surprising because they are thought to result primarily from major fluctuations in peak-to-trough plasma concentrations that are encountered more frequently in agents with a more rapid onset and shorter duration of action than amlodipine. In addition, it was demonstrated that amlodipine has a lower incidence of withdrawals from therapy due to adverse events than has nitrendipine, nifedipine retard (PA), and felodipine at doses that provide similar reductions in blood pressure. The results from these studies suggest that amlodipine is well tolerated and may improve patient compliance.
BENEFITS OF CALCIUM CHANNEL BLOCKERS

FOR THE TREATMENT OF

POST TRANSPLANTATION HYPERTENSION

It has been mentioned earlier that calcium channel blockers may be useful as first-line therapy of post transplantation hypertension. In a recent double-blind crossover study, a significant reduction in blood pressure was achieved with 10 mg amlodipine in hypertensive cyclosporine-treated adult renal transplant patients\textsuperscript{126}. Hypertension has been shown to cause renal impairment and cause damage to the glomeruli of the kidney\textsuperscript{127}. There is increasing evidence that calcium channel blockers are useful as an antihypertensive agent since they have beneficial effects on the kidney\textsuperscript{128-131}.

**Kidney Function**

The renoprotective effects of amlodipine and other calcium channel blockers appear to result, in part, from a selective dilation of the preglomerular blood vessels (i.e., afferent arteriole) that results in an increase in GFR under experimental conditions when isolated perfused kidneys were preconstricted with the potent vasoconstrictor angiotensin II\textsuperscript{132,133}.

In a clinical setting, it was demonstrated that the GFR usually increased while serum creatinine levels dropped, when patients were treated with
amlodipine. Another clinical study found that therapeutically relevant amlodipine doses had no effect on filtration fraction even while renal vascular resistance decreased by as much as 25%.

Moreover, it has also been shown that effective renal blood flow is unaltered following a significant reduction in the renal perfusion pressure by amlodipine and other calcium channel blockers. Thus, there is strong evidence that normal kidney function and renal blood flow is preserved during amlodipine treatment which makes it useful for treatment of hypertension following transplantation and in patients with renal impairment (e.g., chronic renal failure). Amlodipine can be safely administered to patients with differing degrees of renal impairment since pharmacokinetic parameters such as elimination half-life, area under the plasma concentration curve, and maximum plasma concentrations are relatively unaffected.

**Natriuretic Effect**

Calcium channel blockers, in contrast to other vasodilators, do not cause sodium and water retention which would be counterproductive in the treatment of hypertension. Amlodipine has been shown recently to have no effect on either plasma or extracellular fluid volume. Specifically, it has been
established that amlodipine has a mild but persistent natriuretic effect at the level of the renal tubule through inhibition of tubular sodium reabsorption\textsuperscript{135}.

**Cellular Protection**

Amlodipine and other calcium channel blockers also provide protection of the kidney through a direct protective effect at the cellular level by decreasing the rate of mesangial cell proliferation. Such proliferation of this cell type in the glomeruli is common in many types of renal disease (e.g. hypertension-induced glomerular injury)\textsuperscript{140}. Other cellular mechanisms postulated and known to mediate the renoprotective functions of calcium channel blockers include a reduction of renal hypertrophy; a reduction in the metabolic activity of the remnant kidney; an amelioration of uremic nephrocalcinosis; a postulated inhibition of pressure-induced calcium entry; and decreased free radical production\textsuperscript{128}.

Furthermore, calcium channel blockers are also useful as antihypertensive therapy in transplant patients since these drugs have been shown to ameliorate the nephrotoxic effects of cyclosporine (e.g., renal ischemic tubular necrosis) that can lead to acute renal failure if untreated\textsuperscript{141,142}. In addition, it has documented that calcium channel blockers may potentiate the efficacy of cyclosporine which presumably leads to improved graft survival\textsuperscript{143}.
TREATMENT OF PEDIATRIC HYPERTENSION

Most antihypertensive agents used in adults are also administered to pediatric patients. Yet, there exists few data regarding the efficacy and long-term safety in this cohort\(^1\). Calcium antagonists are in widespread use in pediatric patients because of the lack of side effects at therapeutic doses\(^2\). In the case of amlodipine, no studies have been published that examine the use of this calcium channel blocker in the pediatric population.

Amlodipine has many advantages over other calcium channel blockers that make it ideal for the once daily dosing in the treatment of hypertension. In addition, there is evidence that amlodipine may be an ideal first-line agent for the specific treatment of hypertension in patients who have undergone organ or marrow transplantation or have an underlying renal disease.

**Potential Advantages of Amlodipine Treatment in Children**

Amlodipine also has other advantages which make it particularly attractive to the pediatric population. First, amlodipine can be formulated as a liquid preparation which is ideal for younger patients who are unable to swallow the tablets of the other commercially available long-acting calcium channel blockers. Furthermore, the commercially available dosage forms may be too high for a given child’s size. All slow-release calcium channel blockers
depend on an intact delivery system for their long duration of action so that the patient must swallow each tablet whole. As a liquid preparation, an amlodipine dose can be fractionated so that more appropriate doses can be administered to a child. Finally, amlodipine may improve patient compliance since it is administered once a day. One aspect of compliance to calcium channel blocker therapy that may be improved in children treated with amlodipine is a potential lower incidence of withdrawals of this drug due to unacceptable adverse effects. Recall that there were fewer withdrawals of amlodipine therapy in adults due to adverse effects than other long-acting calcium channel blockers.

The purpose of this thesis was to examine the efficacy of amlodipine in pediatric patients and to describe the drug's short-term safety by two experimental approaches. In the first part of the thesis the institutional experience with amlodipine at the Hospital for Sick Children (Toronto, Ontario) was examined by conducting a retrospective study in both transplant patients and individuals with underlying renal abnormalities. The second part of the thesis will again focus on this institutional experience with amlodipine but a more selective transplant cohort was examined. Finally, a prospective study has been conducted involving pediatric renal transplant patients to examine the efficacy, safety, and effect of this agent on patient compliance.
2. PART I: EFFICACY AND SAFETY OF AMLODIPINE IN PEDIATRIC TRANSPLANT AND NEPHROLOGY PATIENTS

HYPOTHESIS: The introduction of amlodipine into an antihypertensive regimen provides as effective blood pressure control as baseline antihypertensive therapy in pediatric patients.

OBJECTIVES:

1.) To compare the efficacy of an antihypertensive regimen that includes amlodipine to baseline treatment for hypertension (i.e. before the inclusion of amlodipine).

2.) To compare common clinical laboratory results before and after the introduction of amlodipine.

3.) To describe the short-term safety of amlodipine in children.
METHODS:

Pharmacy records at the Hospital for Sick Children were reviewed to identify inpatients who had received amlodipine for treatment of hypertension during the period of July 1993-July 1995. The hospital charts of each patient identified were reviewed and the following information was collected before and during amlodipine therapy: age, weight, diagnosis most likely related to the patient's hypertension; indications for amlodipine, temporally related adverse events, systolic and diastolic blood pressure during hospitalization, dosages of amlodipine and concomitant medications, and various clinical laboratory parameters (serum creatinine, hemoglobin concentration, hematocrit percentage, platelet and white blood cell counts, and serum K+ and Na+ concentrations).

Amlodipine was administered to all patients in the second period of analysis. This agent either replaced one or more antihypertensive drugs or was added onto the patient's pre-existing antihypertensive regimen. The period of analysis prior to the introduction of amlodipine was referred to as the baseline treatment period (i.e. it includes a patient's antihypertensive regimen in the absence of amlodipine). The doses of each antihypertensive agent in the baseline treatment period were raised in a stepwise manner to clinically acceptable maximum levels in order to control each child's blood pressure. If
such blood pressure control was not achieved. Amlodipine therapy was then introduced. In most children in this study, amlodipine was introduced for reasons of convenience and not because of poor blood pressure control. The blood pressure data before and during amlodipine therapy corresponds to the maximum dose(s) of antihypertensive agents used.

The blood pressure was measured by nurses on the various hospital wards using a Dinamap monitor (Critikon, Inc.) with a Dura cuff (Medicare, Inc.) for most patients. However, Hewlett Packard electrocardiogram units with calibrated V-Lok cuffs (W.A. Baum Co.) were also used in the cardiac transplant patients to observe their cardiac function. Typically, blood pressure measurements were recorded six times per day (i.e., every 4 hours), but this number varied from three to fifteen depending on the status of the child’s blood pressure on a given day. Manual blood pressure readings were occasionally taken with a Tycos sphygmomanometer to confirm the accuracy of a given measurement.

The “overall” mean systolic (SBP) and diastolic blood pressure (DBP) measurements of each patient were calculated in both periods of analysis (i.e., before and following the introduction of amlodipine). The “overall” mean blood pressure was defined as the average of the mean daily blood pressure readings calculated for each patient in both periods of analysis. The “overall”
means (SBP and DBP) of each patient for the analysis periods before and following amlodipine treatment were compared using Student’s paired t-tests. Patients were included in this retrospective study if at least 3 days of blood pressure data were available for each period of analysis (i.e. before and during the commencement of amlodipine therapy). Comparisons of the means of each individual clinical laboratory parameter prior to and during amlodipine administration were also conducted. Statistical comparisons were performed using a Student’s paired t-test (Sigmastat®). The data is presented as mean ± SEM.

RESULTS:

Pediatric Transplant and Nephrology Patient Characteristics (Table I):

Twenty-three of the twenty-eight patients identified through the use of pharmacy records had sufficient blood pressure data to be included in this study but two of the younger patients did not have any recorded diastolic blood pressure readings. The general characteristics of each patient are listed in Table I. The median age of the cohort was 7 years (range: 2 weeks to 17 years) and included 16 males. The underlying diseases of the cohort were heterogeneous in nature but involved a large number of patients with
underlying renal abnormalities. Almost half of the patients had received an organ or bone marrow transplant. All patients were receiving antihypertensive therapy prior to the introduction of amlodipine. The dose of this calcium channel blocker was administered orally, once-a-day in all 23 patients. Amlodipine was used as replacement for other calcium channel blockers (e.g., nifedipine) in 19 individuals. The mean initial amlodipine dose used to initiate therapy was 0.14 ± 0.01 mg/kg/day (range: 0.05 to 0.24). An increase in amlodipine dose was required in ten (43%) patients which resulted in a mean maximal dose of 0.22 ± 0.03 mg/kg/day (range: 0.08 to 0.66). A Student's paired t-test demonstrated that a significant difference existed between the mean initial and maximum amlodipine dosage (p = 0.01).

Blood Pressure (Table II):

Using Student’s paired t-test, the mean SBP and DBP were significantly lower following the introduction of amlodipine as compared to baseline antihypertensive therapy (2.5 ± 1.1 mm Hg and 3.1 ± 1.5 mm Hg, respectively; p < 0.05). Following the introduction of amlodipine, fifteen out of 23 (65%) patients each experienced a mean decrease in SBP while 15 out of 21 patients (71%) had a mean reduction in DBP.
Laboratory Data (Table III):

There were no significant changes in mean hematocrit percentage, mean serum concentrations of creatinine, potassium, sodium, and hemoglobin, nor in mean platelet and leukocyte counts following the initiation of amlodipine therapy. However, there was a clinically nonsignificant upward trend in serum potassium and downward trend in the leukocyte count.

Adverse Drug Reactions:

There were no adverse drug reactions temporally associated with amlodipine therapy in the majority of patients. However, one patient developed a urticarial rash during amlodipine treatment which subsided despite the continuation of this calcium channel blocker.
<table>
<thead>
<tr>
<th>Patient Number</th>
<th>Age (Yrs)</th>
<th>Gender</th>
<th>Diagnosis</th>
<th>Antihypertensives Prior to Amlodipine</th>
<th>Amlodipine Dose (mg/kg/d)</th>
<th>Initial/Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.1</td>
<td>M</td>
<td>Chronic Renal Failure</td>
<td>Furosemide</td>
<td></td>
<td>0.21/0.21</td>
</tr>
<tr>
<td>2</td>
<td>0.6</td>
<td>M</td>
<td>AHUS</td>
<td>Felodipine*</td>
<td></td>
<td>0.08/0.25</td>
</tr>
<tr>
<td>3</td>
<td>0.8</td>
<td>M</td>
<td>Renal Transplant</td>
<td>Nif-PA*, Nadolol*</td>
<td></td>
<td>0.16/0.42</td>
</tr>
<tr>
<td>4</td>
<td>1</td>
<td>M</td>
<td>BPD</td>
<td>Hydralazine*, HCTZ</td>
<td></td>
<td>0.15/0.15</td>
</tr>
<tr>
<td>5</td>
<td>1</td>
<td>F</td>
<td>Chronic Renal Failure</td>
<td>Nif-SA*, Captopril*</td>
<td></td>
<td>0.14/0.14</td>
</tr>
<tr>
<td>6</td>
<td>1</td>
<td>M</td>
<td>Bone Marrow Transplant</td>
<td>Labetolol*</td>
<td></td>
<td>0.21/0.21</td>
</tr>
<tr>
<td>7</td>
<td>2</td>
<td>M</td>
<td>Heart Transplant</td>
<td>Nif-SA*, Furosemide</td>
<td></td>
<td>0.16/0.16</td>
</tr>
<tr>
<td>8</td>
<td>2</td>
<td>M</td>
<td>ECMO</td>
<td>Nif-SA*</td>
<td></td>
<td>0.08/0.08</td>
</tr>
<tr>
<td>9</td>
<td>3</td>
<td>F</td>
<td>Heart Transplant</td>
<td>Nif-SA*</td>
<td></td>
<td>0.17/0.17</td>
</tr>
<tr>
<td>10</td>
<td>4</td>
<td>M</td>
<td>Chronic Renal Failure</td>
<td>Nif-SA*, Captopril*</td>
<td></td>
<td>0.13/0.13</td>
</tr>
<tr>
<td>11</td>
<td>7</td>
<td>M</td>
<td>Renal Transplant</td>
<td>Nif-XL*</td>
<td></td>
<td>0.13/0.22</td>
</tr>
<tr>
<td>12</td>
<td>7</td>
<td>M</td>
<td>Renal Transplant</td>
<td>Nif-SA*</td>
<td></td>
<td>0.22/0.66</td>
</tr>
<tr>
<td>13</td>
<td>8</td>
<td>F</td>
<td>Bone Marrow Transplant</td>
<td>Nif-PA*</td>
<td></td>
<td>0.14/0.14</td>
</tr>
<tr>
<td>14</td>
<td>9</td>
<td>F</td>
<td>Renal Artery Stenosis</td>
<td>Nif-PA*, Nadolol, HCTZ</td>
<td></td>
<td>0.09/0.56</td>
</tr>
<tr>
<td>15</td>
<td>10</td>
<td>M</td>
<td>Renal Transplant</td>
<td>Nif-XL*</td>
<td></td>
<td>0.21/0.21</td>
</tr>
<tr>
<td>16</td>
<td>10</td>
<td>M</td>
<td>Chronic Renal Failure</td>
<td>Nif-SA*</td>
<td></td>
<td>0.07/0.13</td>
</tr>
<tr>
<td>17</td>
<td>12</td>
<td>F</td>
<td>Heart Transplant</td>
<td>Enalapril*, Furosemide</td>
<td></td>
<td>0.18/0.18</td>
</tr>
<tr>
<td>18</td>
<td>12</td>
<td>M</td>
<td>Renal Transplant</td>
<td>Nif-XL*</td>
<td></td>
<td>0.10/0.10</td>
</tr>
<tr>
<td>19</td>
<td>12</td>
<td>M</td>
<td>Glomerulonephritis</td>
<td>Nif-PA*</td>
<td></td>
<td>0.08/0.16</td>
</tr>
<tr>
<td>20</td>
<td>12</td>
<td>F</td>
<td>Renal Transplant</td>
<td>Nif-PA*</td>
<td></td>
<td>0.10/0.10</td>
</tr>
<tr>
<td>21</td>
<td>16</td>
<td>M</td>
<td>Chronic Renal Failure</td>
<td>Nif-XL*, Hydralazine</td>
<td></td>
<td>0.05/0.15</td>
</tr>
<tr>
<td>22</td>
<td>16</td>
<td>M</td>
<td>Renal Transplant</td>
<td>Nif-PA*</td>
<td></td>
<td>0.10/0.15</td>
</tr>
<tr>
<td>23</td>
<td>17</td>
<td>F</td>
<td>Chronic Renal Failure</td>
<td>Nif-PA*, Hydralazine</td>
<td></td>
<td>0.24/0.36</td>
</tr>
</tbody>
</table>

* discontinued with amlodipine therapy; Nif, nifedipine; SA, short-acting; PA, prolonged action; XL, extended release; HCTZ, hydrochlorothiazide; ECMO, extracorporeal membrane oxygenation; BPD, bronchopulmonary dysplasia; AHUS, atypical hemolytic uremic syndrome
# Table II: Blood Pressure (Mean ± SEM)

<table>
<thead>
<tr>
<th></th>
<th>Before Amlodipine</th>
<th>During Amlodipine</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(mm Hg)</td>
<td>(mm Hg)</td>
<td></td>
</tr>
<tr>
<td>Systolic Blood</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pressure (n=23)</td>
<td>126.7 ± 2.9</td>
<td>124.2 ± 2.7</td>
<td>0.02*</td>
</tr>
<tr>
<td>Diastolic Blood</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pressure (n=21)</td>
<td>80.2 ± 2.4</td>
<td>77.1 ± 2.7</td>
<td>0.02**</td>
</tr>
</tbody>
</table>

*: ** p-value was based on a Student’s paired t-test in both cases
<table>
<thead>
<tr>
<th></th>
<th>Before Amlodipine (n=18)</th>
<th>During Amlodipine (n=18)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium (mmol/L)</td>
<td>137 ± 0.8</td>
<td>137 ± 0.6</td>
<td>0.79</td>
</tr>
<tr>
<td>Potassium (mmol/L)</td>
<td>3.9 ± 0.1</td>
<td>4.1 ± 0.1</td>
<td>0.05</td>
</tr>
<tr>
<td>Creatinine (μmol/L)</td>
<td>175 ± 49.7</td>
<td>162 ± 55.6</td>
<td>0.60</td>
</tr>
<tr>
<td>Leukocytes (10^9/L)</td>
<td>10.3 ± 1.3</td>
<td>8.1 ± 1.0</td>
<td>0.05</td>
</tr>
<tr>
<td>Platelets (10^9/L)</td>
<td>282 ± 45.8</td>
<td>280 ± 40.4</td>
<td>0.95</td>
</tr>
<tr>
<td>Hemoglobin (g/L)</td>
<td>109 ± 4.1</td>
<td>106 ± 3.9</td>
<td>0.44</td>
</tr>
<tr>
<td>Hematocrit (%)</td>
<td>33 ± 1.3</td>
<td>32 ± 1.2</td>
<td>0.38</td>
</tr>
</tbody>
</table>
3. PART II: EFFICACY AND SAFETY OF AMLODIPINE IN PEDIATRIC BONE MARROW TRANSPLANT PATIENTS

A second retrospective study was conducted on a more selective pediatric cohort to determine if the positive results with regards to the efficacy of amlodipine in the first retrospective study were reproducible. The cohort examined here was more homogeneous than the first since all patients had undergone a similar medical procedure (i.e. bone marrow transplantation) and presumably were subject to more similar pharmacological strategies to treat their hypertension since it developed following the use of cyclosporine and corticosteroids.

**HYPOTHESIS:** The incorporation of amlodipine into an antihypertensive regimen provides blood pressure control similar to that of baseline therapy in pediatric bone marrow transplant patients.

**OBJECTIVES:**

1.) To compare the efficacy of an antihypertensive regimen that includes amlodipine to baseline therapy before the introduction of this calcium channel blocker.

2.) To describe the short-term safety of amlodipine.
**METHODS:**

Thirteen pediatric bone marrow transplant inpatients who had received amlodipine treatment at the Hospital for Sick Children were identified using pharmacy records. The patients' charts were then reviewed and the period of analysis of antihypertensive therapy ranged from May 1994 to June 1996 and encompassed periods before and during amlodipine treatment. The following information was extracted for each patient: age; weight; condition responsible for bone marrow transplantation; indications for the use of amlodipine; systolic blood pressure (SBP) and diastolic blood pressure (DBP) measurements, and adverse events recorded during amlodipine treatment. The results of two bone marrow transplant patients reviewed in the first retrospective study (refer to Table I) were pooled with the remaining 13 patients to bring the cohort sample size of this study to 15. The standard techniques and equipment used by the nurses to measure blood pressure data are the same as those listed in the methods section of the first retrospective study (page 30).

As in the first retrospective study, the mean SBP and DBP measurements of each patient were used for comparison of the efficacy of the two treatment periods: before and during amlodipine therapy. However, in contrast to the initial retrospective study, the period of analysis before amlodipine was standardized for each patient to the three days immediately prior to its
introduction since this was likely the timeframe when the patient may have been hypertensive and the physician was contemplating whether to substitute amlodipine for another blood pressure-reducing agent or to incorporate it into the antihypertensive regimen.

Furthermore, the amlodipine treatment analysis period in this second study was set to begin from the fifth day following the commencement of amlodipine therapy since, in children, it should theoretically take about one week for steady state levels of amlodipine to be reached in the plasma resulting in clinically relevant reductions in blood pressure. The fifth day into amlodipine treatment (as opposed to the seventh day) was chosen as a starting point in order to allow for a minimum of at least 3 days of blood pressure data for each of our patients. It is a reasonable trade-off since amlodipine levels at the fifth day should be fairly close to steady state levels. The blood pressure data are presented as cohort mean ± SEM. Individual mean blood pressure measurements are also displayed in each analysis period for each child. Statistical comparisons of SBP and DBP were conducted using Student’s paired t-tests (Sigmastat®).
RESULTS:

Characteristics of Pediatric Bone Marrow Transplant Patients (Table IV):

The median age of the patient cohort examined in this study was eight years (range: 1 to 17 years); nine children were female. Amlodipine was administered as an oral once daily dose to all patients. The mean initial dose of amlodipine used for the treatment of hypertension was $0.12 \pm 0.01$ mg/kg/day. Four patients required an increase in amlodipine dosage, which resulted in a mean maximum dose of $0.16 \pm 0.02$ mg/kg/day. Patient # 13 was given a loading dose of 10 mg on the first day of treatment and received maintenance doses of 5 mg per day thereafter. A Student's paired t-test demonstrated that a significant difference existed between mean initial and maximal amlodipine dosage ($p = 0.03$).

Antihypertensive Regimen Prior to and During Amlodipine:

In six patients, amlodipine was the sole antihypertensive drug used, while in the remaining cases the drug was used in combination with other blood pressure-lowering drugs. Amlodipine replaced a single calcium channel blocker in six cases whereas in another child it was substituted for two calcium channel blockers. Amlodipine also replaced a diuretic in one case and an ACE inhibitor in another. Furthermore, this drug replaced both a calcium channel
blocker and diuretic in one individual and replaced a β-blocker and calcium channel blocker in another child. Moreover, amlodipine was also introduced in one patient to replace both a vasodilator and diuretic, while in another child it was administered in combination with an ACE inhibitor to replace two calcium channel blockers and a vasodilator. Finally, in two cases this calcium channel blocker was added to each patient’s antihypertensive regimen.

**Blood Pressure (Table V):**

Eleven of the fifteen patients (73%) had an overall individual reduction in both systolic and diastolic blood pressure following the introduction of amlodipine (maximum dose) for the treatment of post-transplantation hypertension. Using Student’s paired t-test, both the mean SBP and DBP were significantly lower in this patient cohort during amlodipine therapy than before its use (6.5 ± 2.7 mm Hg and 5.9 ± 2.7 mm Hg, respectively; p < 0.05). Note in table V that z scores are also given for each patient’s mean blood pressure (SBP and DBP) before and during amlodipine therapy. The z score indicates the relative percentage by which each patient’s mean blood pressure exceeds (positive values) the 95th blood pressure percentile for his/her age and gender. A Negative z score indicates the relative percentage in which a patient’s mean blood pressure appears below his/her corresponding 95th percentile for blood pressure.
Adverse Drug Events:

Two patients experienced ankle edema during amlodipine therapy that failed to respond to diuretic therapy (novospirozone). This adverse event led to the discontinuation of amlodipine treatment in both individuals (patients 1 and 3). The ankle edema subsided in both children approximately 2 to 3 days after the cessation of amlodipine therapy.
### Table IV: Characteristics of Pediatric Bone Marrow Transplant Patients

<table>
<thead>
<tr>
<th>Patient Number</th>
<th>Gender</th>
<th>Age (Yrs)</th>
<th>Weight (kg)</th>
<th>Diagnosis</th>
<th>Amlodipine Dose (mg/kg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>1</td>
<td>11</td>
<td>Severe Combined Immunodeficiency</td>
<td>0.09/0.09</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>1</td>
<td>12</td>
<td>Acute Lymphoblastic Leukemia</td>
<td>0.21/0.21</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>1</td>
<td>13</td>
<td>Chediak-Higashi Syndrome</td>
<td>0.08/0.08</td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>2</td>
<td>19</td>
<td>Severe Combined Immunodeficiency</td>
<td>0.21/0.21</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>2</td>
<td>12</td>
<td>Hurler’s Syndrome</td>
<td>0.10/0.25</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>5</td>
<td>18</td>
<td>Neuroblastoma</td>
<td>0.14/0.14</td>
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<tr>
<td>7</td>
<td>F</td>
<td>8</td>
<td>25</td>
<td>Fanconi’s Anemia</td>
<td>0.10/0.10</td>
</tr>
<tr>
<td>8</td>
<td>F</td>
<td>8</td>
<td>35</td>
<td>Aplastic Anemia</td>
<td>0.14/0.14</td>
</tr>
<tr>
<td>9</td>
<td>F</td>
<td>10</td>
<td>27</td>
<td>Aplastic Anemia</td>
<td>0.09/0.09</td>
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<tr>
<td>10</td>
<td>F</td>
<td>11</td>
<td>30</td>
<td>Chronic Myelogenous Leukemia</td>
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</tr>
<tr>
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<td>F</td>
<td>12</td>
<td>32</td>
<td>Schwachman-Diamond Syndrome</td>
<td>0.08/0.08</td>
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<tr>
<td>12</td>
<td>M</td>
<td>14</td>
<td>41</td>
<td>Aplastic Anemia</td>
<td>0.12/0.12</td>
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<tr>
<td>13</td>
<td>F</td>
<td>15</td>
<td>46</td>
<td>Acute Myelogenous Leukemia</td>
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<tr>
<td>14</td>
<td>M</td>
<td>16</td>
<td>67</td>
<td>Acute Lymphoblastic Leukemia</td>
<td>0.07/0.21</td>
</tr>
<tr>
<td>15</td>
<td>F</td>
<td>17</td>
<td>67</td>
<td>Acute Lymphoblastic Leukemia</td>
<td>0.07/0.11</td>
</tr>
</tbody>
</table>
**Table V: Mean Blood Pressure and Z Scores**

**Before and During Amlodipine Therapy**

<table>
<thead>
<tr>
<th>Patient Number</th>
<th>Pre-amlodipine SBP (mm Hg)</th>
<th>Percentage</th>
<th>Post-amlodipine SBP (mm Hg)</th>
<th>Percentage</th>
<th>Pre-amlodipine DBP (mm Hg)</th>
<th>Percentage</th>
<th>Post-amlodipine DBP (mm Hg)</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>122.5 [-11.4]</td>
<td></td>
<td>115.2 [4.7]</td>
<td></td>
<td>77.5 [4.7]</td>
<td></td>
<td>77.3 [4.5]</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>109.1 [-0.8]</td>
<td></td>
<td>111.2 [1.1]</td>
<td></td>
<td>64.5 [-12.8]</td>
<td></td>
<td>65.2 [-11.9]</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>116.2 [5.6]</td>
<td></td>
<td>114.4 [4.0]</td>
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<td>75.5 [4.9]</td>
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<td>73.9 [2.6]</td>
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<td>79.2 [8.5]</td>
<td></td>
<td>85.3 [16.8]</td>
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</tr>
<tr>
<td>6</td>
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<td></td>
<td>101.3 [-11.1]</td>
<td></td>
<td>77.9 [5.3]</td>
<td></td>
<td>58.9 [-20.4]</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>120.9 [4.2]</td>
<td></td>
<td>115.3 [-0.7]</td>
<td></td>
<td>78.8 [5.1]</td>
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<td>73.9 [-1.5]</td>
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</tr>
<tr>
<td>8</td>
<td>126.6 [9.1]</td>
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<td>108.8 [-6.2]</td>
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<td></td>
<td>85.0 [6.3]</td>
<td></td>
<td>81.7 [2.1]</td>
<td></td>
</tr>
<tr>
<td>11</td>
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<td></td>
<td>121.2 [-3.0]</td>
<td></td>
<td>83.6 [2.0]</td>
<td></td>
<td>79.4 [-3.2]</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>129.7 [-0.2]</td>
<td></td>
<td>104.0 [-20.0]</td>
<td></td>
<td>91.0 [11.0]</td>
<td></td>
<td>66.0 [-19.5]</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>128.1 [-0.7]</td>
<td></td>
<td>124.2 [-3.7]</td>
<td></td>
<td>84.1 [-1.1]</td>
<td></td>
<td>80.0 [-5.9]</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>144.9 [8.1]</td>
<td></td>
<td>123.6 [-7.8]</td>
<td></td>
<td>84.4 [-0.7]</td>
<td></td>
<td>58.9 [-30.7]</td>
<td></td>
</tr>
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<td></td>
<td>119.5 [-8.1]</td>
<td></td>
<td>78.3 [-7.9]</td>
<td></td>
<td>83.6 [-1.6]</td>
<td></td>
</tr>
</tbody>
</table>

Mean 123.5 ± 2.1* 117.2 ± 2.2* 81.5 ± 1.8** 75.5 ± 2.6**

* p-value < 0.05 (Student’s paired t-test) ** p-value < 0.05 (Student’s paired t-test)

SBP, systolic blood pressure; DBP, diastolic blood pressures

Note: numeric values in parentheses represent z score of mean blood pressures relative to the 95th percentile for each patient’s age and gender.
4. PART III: PROSPECTIVE STUDY OF THE EFFICACY OF AMLODIPINE IN PEDIATRIC RENAL TRANSPLANT PATIENTS

**HYPOTHESIS:** Amlodipine controls blood pressure in hypertensive pediatric renal transplant patients as effectively as nifedipine or felodipine.

**OBJECTIVES:**

1) To investigate the efficacy of amlodipine in controlling elevated blood pressure as compared to nifedipine or felodipine.

2) To compare the patient's compliance between amlodipine and nifedipine/felodipine.

3) To describe the safety of amlodipine, nifedipine, and felodipine.

**PATIENTS:**

Eleven patients between the ages of 3 and 18 years were recruited from the nephrology outpatient clinic at the Hospital for Sick Children.
INCLUSION CRITERIA:

1) Written and verbal informed consent.
2) Patient was receiving either nifedipine or felodipine for treatment of hypertension prior to his/her participation in this study.
3) Patient had stable blood pressure control as defined as no change in antihypertensive medications or dosages during the month prior to recruitment.
4) Patient had received a renal transplant at least 3 months prior to recruitment.

EXCLUSION CRITERIA:

1.) Known allergy to amlodipine, nifedipine, or felodipine.

METHODS:

The study comprised two treatment phases: amlodipine and nifedipine (or felodipine). No patients had never received amlodipine for treatment of hypertension. In a randomized, cross-over design each subject received amlodipine and nifedipine (or felodipine) in separate 30 day treatment periods. Using a random table, the first treatment period (amlodipine or nifedipine/felodipine) was randomized before the start of the study. Thus, some would receive amlodipine therapy first while other patients would start the study with nifedipine or felodipine. There was no washout period between
each treatment phase and the patients and investigator were unblinded as to which medication was being administered.

**Dosing Procedure:**

**Amlodipine:**

Amlodipine (Norvasc™, Pfizer) is commercially available in 2.5, 5 (scored), and 10 mg tablets. Patients in the nephrology clinic at our institution are typically administered an initial amlodipine dose of 0.10 mg/kg once a day. An exact initial dose to match a patient’s body weight can be achieved by dissolving an amlodipine tablet in water using a dissolvant dose container. The standard procedure involves dissolving a 5 mg tablet in 5 mL of water. The appropriate dose (volume) is then obtained from the dissolved solution (each mL contains 1 mg) using a syringe and the remainder of the solution is discarded. The practice of obtaining a smaller dose is necessary for very young patients (e.g. newborns) who cannot swallow the amlodipine tablets or who require a dose smaller than one tablet to match their body weight. Since all of the patients recruited in this study were older and did not fit the aforementioned criteria (i.e., unable to swallow amlodipine tablets, tablet dose inappropriate for size), each was administered a single intact tablet dose which was approximately 0.1 mg/kg.
Patients received either an initial single daily 2.5 mg tablet or a maximum initial single daily 5mg tablet. If the patient’s blood pressure was not in the normotensive range (< 95th percentile for age) after approximately 5 to 7 days of amlodipine therapy, the staff nephrologist was informed by the patient’s parent and it was decided whether to raise the amlodipine dose by 50 to 100%. The maximum daily dose permitted by this study was 10 mg. The primary investigator was blinded to any dose changes ordered by the staff nephrologist.

**Nifedipine or Felodipine:**

Since each patient recruited was receiving either nifedipine or felodipine prior to his/her participation in the study, no dose changes were necessary for either calcium channel blocker during the study. The appropriate daily doses had been previously determined by the staff nephrologist so as to obtain blood pressure measurements in the normotensive range (< 95th percentile for age).

**Blood Pressure Monitoring:**

Blood pressure was monitored at home manually with either a mercury sphygmomanometer or an automated oscillometric device (Critikon Inc., Tampa Fla.). The adult caregiver (parent) of each patient was instructed to take
blood pressure measurements twice daily (one measurement in the morning and another in the evening at approximately the same times). Each parent had been properly trained by a nurse to measure the child’s blood pressure using a standardized technique with the patient in the supine position. To measure blood pressure accurately, it is critical to use the appropriate cuff size. For example, the use of a cuff that is too small will give false high blood pressure readings. The cuff must be wide enough so that the bladder completely encircles the circumference of the patient’s arm and wide enough to cover approximately three quarters of the upper arm between the olecranon and the top of the shoulder. There must be sufficient room at the antecubital fossa to place the stethoscope there comfortably if a mercury sphygmomanometer is used. The cuff should not be placed too high around the upper arm so as to obstruct the patient’s axilla.

During the final 2 weeks of each treatment phase, ambulatory blood pressure monitoring was also performed over a 24-hour interval using either a Takeda blood pressure monitor model TM 2420 (A & D Engineering Inc., California) or an ambulatory blood pressure monitor model 90207 (Spacelabs Medical, Mississauga, ON). Each monitor was preset to measure the blood pressure every 30 minutes, from 9 A.M. to 10 P.M., and every 60 minutes from 10 P.M. to 9 A.M. The patient’s heart rate was also recorded during these two
intervals. For the majority of patients, the blood pressure monitors were properly placed on the patient directly by the trained investigator. However, patients who lived outside of Metropolitan Toronto were given a demonstration of the proper set-up while attending the nephrology outpatient clinic at the Hospital for Sick Children. At the appropriate time, the monitors were later shipped at the appropriate time to each patient’s residence, with an instructional video detailing the standard set-up of the monitoring equipment. Each patient was supplied with a 24 hour diary to record his/her activities throughout the monitoring period.

In order to ensure consistent blood pressure readings were obtained during ambulatory blood pressure monitoring, the patient was instructed to remain still during each measurement. Blood pressure measurements are also influenced by the arm position. There is an approximate increase of 10 to 12 mm Hg in both systolic and diastolic blood pressure as the arm is lowered from the outstretched position perpendicular to the trunk to a arm position parallel to the trunk. As a result, each patient was instructed to place the arm parallel to the trunk for each blood pressure measurement. Furthermore, patients were also instructed not to talk during a blood pressure measurement since this is a potent pressor stimulus. For example, reading aloud has been shown to cause
an immediate increase in blood pressure of about 10/7 mm Hg in normotensive subjects which subsides immediately after the individuals stop reading\textsuperscript{147,148}.

In both the twice-daily manual and 24 hour blood pressure measuring techniques the cuff was placed on the left upper arm of the patient.

Adverse Events:

Each patient was instructed to record any adverse events experienced each day throughout the study.

Compliance:

Compliance was assessed using the Medication Event Monitoring System (MEMS. Aprex. California). The MEMS® TrackCap\textsuperscript{TM} is a medication bottle cap that contains a microelectronic tracking device. This electronic chip in the lid of the cap records the date and time when a medication bottle containing a study drug was opened. The parents and children were not aware of the purpose of this electronic monitoring device.

Statistics:

With mean diastolic blood pressure as a primary endpoint, a sample of eleven patients will be sufficient to show a median effect size difference in blood pressure between the two drugs with an alpha of 0.05 and a power of
80%. The median effect size that will be considered significant will be any value greater than 10 mm Hg. Amlodipine will be compared to nifedipine (or felodipine) with respect to: mean systolic and diastolic blood pressure (30 day) at home, mean systolic and diastolic blood pressure (day and night) by 24-hour ambulatory blood pressure monitoring. The rate of compliance will be compared between the two drugs in five patients. All comparisons will be performed using Student's paired t-tests (Sigmastat®).

RESULTS:

Characteristics of Pediatric Renal Transplant Patients (Table VI):

The median age of the cohort was 16 years (range: 9 to 17) and the study included six boys and five girls. All patients but one (patient 8) had undergone renal transplantation. The mean initial dose of amlodipine used was 0.09 ± 0.01 mg/kg/day. Four patients required an increase in amlodipine dosage so that the mean maximal amlodipine dosage was 0.12 ± 0.02 mg/kg/day. A Student's paired t-test demonstrated that no significant difference was evident between mean initial and maximum amlodipine dosage (p = 0.06). Six patients were treated only with a single calcium channel blocker throughout the study whereas the remaining individuals had combination therapy. The additional antihypertensive medication(s) used by these five patients were not calcium
channel blockers class and the dosages of these drugs were identical in each treatment phase of the study.

**Blood Pressure Control:**

1. **Home 30-Day Mean Blood Pressure (Table VII):**

   Using Student’s paired t-tests there was not a significant difference in both the cohort’s mean 30-day systolic blood pressure and mean 30-day diastolic blood pressure when comparing the two treatment phases (amlodipine and nifedipine/felodipine). Eight patients had a reduction in their individual mean SBP with amlodipine therapy, whereas six patients experienced a lower mean DBP during this treatment phase.

2. **Twenty-four Hour Blood Pressure:**

   Nine of the eleven patients completed 24-hour blood pressure monitoring for both drug treatment periods.

   **A) Day time Blood Pressure:**

   Using Student’s paired t-tests, there was no statistical difference in mean daytime (9 A.M.-10 P.M.) systolic blood pressure (amlodipine: 126.6 ± 3.4 mm Hg; nifedipine/felodipine: 127.5 ± 3.4 mm Hg; p = 0.78). In addition, there was no statistical difference in mean daytime diastolic blood pressure (amlodipine: 78.6 ± 2.2 mm Hg; nifedipine/felodipine: 77.5 ± 2.2 mm Hg; p = 0.65).
B) Nighttime Blood Pressure:

No statistical mean difference was found between each treatment period for the patients in nighttime systolic blood pressure (amlodipine: 119.5 ± 2.9 mm Hg; nifedipine/felodipine: 119.3 ± 3.3 mm Hg; \( p = 0.96 \)). Furthermore, no statistical mean difference was observed in the nighttime diastolic blood pressure (amlodipine: 74.7 ± 3.2 mm Hg; nifedipine/felodipine: 74.5 ± 3.4 mm Hg; \( p = 0.95 \)).

Adverse Events:

No adverse events were reported by the patients during the two calcium channel blocker treatment periods.

Compliance:

There was no significant difference between the two calcium channel blocker treatment periods in mean patient compliance (i.e. percentage of drug taken versus prescribed amount) during each 30-day assessment period between the two calcium channel blocker treatment periods (amlodipine: 93.4 ± 1.7 %; nifedipine/felodipine: 93.4 ± 1.6 %; \( p = 0.94 \), Student’s paired t-test).
## Table VI: Characteristics of Pediatric Renal Transplant Patients

<table>
<thead>
<tr>
<th>Patient Number</th>
<th>Age (Yrs)</th>
<th>Gender</th>
<th>Weight (kg)</th>
<th>Renal Diagnosis</th>
<th>Amlodipine Dosage (mg/kg/day) Initial/Max</th>
<th>Ca&lt;sup&gt;2+&lt;/sup&gt; Channel Blocker Therapy Prior to Amlodipine</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>9</td>
<td>F</td>
<td>35</td>
<td>Focal Segmental Glomerulosclerosis</td>
<td>0.07/0.07</td>
<td>Nifedipine PA 20 mg o.d.</td>
</tr>
<tr>
<td>2</td>
<td>10</td>
<td>M</td>
<td>27</td>
<td>Autosomal Dominant Polycystic Kidney Disease</td>
<td>0.10/0.10</td>
<td>Nifedipine XL 30 mg o.d.</td>
</tr>
<tr>
<td>3</td>
<td>12</td>
<td>M</td>
<td>30</td>
<td>Renal Dysplasia</td>
<td>0.08/0.08</td>
<td>Nifedipine XL 30 mg o.d.</td>
</tr>
<tr>
<td>4</td>
<td>14</td>
<td>M</td>
<td>37</td>
<td>Cystinosis</td>
<td>0.07/0.07</td>
<td>Felodipine E.R. 15 mg o.d.</td>
</tr>
<tr>
<td>5</td>
<td>16</td>
<td>M</td>
<td>45</td>
<td>Cystinosis</td>
<td>0.11/0.11</td>
<td>Felodipine E.R. 10 mg o.d.</td>
</tr>
<tr>
<td>6</td>
<td>16</td>
<td>F</td>
<td>46</td>
<td>Radiation-induced Nephritis</td>
<td>0.11/0.22</td>
<td>Nifedipine XL 30 mg b.i.d.</td>
</tr>
<tr>
<td>7</td>
<td>16</td>
<td>M</td>
<td>72</td>
<td>Alport’s Syndrome</td>
<td>0.07/0.10</td>
<td>Nifedipine XL 30 mg b.i.d.</td>
</tr>
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<td>8</td>
<td>16</td>
<td>F</td>
<td>90</td>
<td>Unknown</td>
<td>0.06/0.11</td>
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<tr>
<td>9</td>
<td>17</td>
<td>F</td>
<td>34</td>
<td>Bilateral Wilm’s Tumour</td>
<td>0.15/0.22</td>
<td>Felodipine ER 10 mg b.i.d.</td>
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<tr>
<td>10</td>
<td>17</td>
<td>F</td>
<td>35</td>
<td>Adult Polycystic Kidney Disease</td>
<td>0.14/0.14</td>
<td>Nifedipine XL 30 mg o.d.</td>
</tr>
<tr>
<td>11</td>
<td>17</td>
<td>M</td>
<td>60</td>
<td>Nephrotic Syndrome</td>
<td>0.08/0.08</td>
<td>Nifedipine XL 30 mg o.d.</td>
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</tbody>
</table>
# Table VII: Home 30-day Mean Blood Pressure

<table>
<thead>
<tr>
<th>Patient Number</th>
<th>S.B.P. During Nifedipine/Felodipine (mm Hg)</th>
<th>S.B.P. During Amlodipine (mm Hg)</th>
<th>D.B.P. During Nifedipine/Felodipine (mm Hg)</th>
<th>D.B.P. During Amlodipine (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>122.8</td>
<td>113.2</td>
<td>74.4</td>
<td>65.8</td>
</tr>
<tr>
<td>2</td>
<td>104.7</td>
<td>105.4</td>
<td>73.3</td>
<td>74.9</td>
</tr>
<tr>
<td>3</td>
<td>113.8</td>
<td>115.6</td>
<td>82</td>
<td>83.8</td>
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<td>4</td>
<td>116.4</td>
<td>114.9</td>
<td>79.8</td>
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<td>79.7</td>
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<td>81.7</td>
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<td>136.1</td>
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<td>73.2</td>
</tr>
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<tr>
<td>11</td>
<td>115.9</td>
<td>114.3</td>
<td>74.8</td>
<td>75.7</td>
</tr>
</tbody>
</table>

Mean: 121.2 ± 3.0*  119.3 ± 2.6*  79.0 ± 1.7**  77.6 ± 1.3**

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* p-value = 0.09 (Student’s paired t-test)

** p-value = 0.27 (Student’s paired t-test)
5. DISCUSSION:

Part I and Part II:

Both retrospective studies demonstrated a statistically significant reduction of both systolic and diastolic blood pressure in children receiving pharmacological treatment for hypertension when amlodipine replaced one or more antihypertensive drugs or was added onto an existing antihypertensive regimen. The majority of pediatric patients in both studies experienced improved blood pressure control during the administration of amlodipine. In certain individual patients (e.g., numbers 12 and 14 in the second retrospective study; table V) the reduction in blood pressure was clinically significant since it moved their blood pressure substantially below the 95th percentile so that these children were no longer considered to be hypertensive. However, in other individuals the change in mean blood pressure was marginal (e.g. patients 2 and 3, table V).

Since both studies were retrospective, it is possible that the apparent difference in blood pressure observed may, in part, be explained by confounding variables between the two periods of analysis, or it may reflect a statistical error due to the limited sample size.
However, evidence in certain individuals strongly suggested that the decrease in blood pressure could be attributed primarily to the effects of amlodipine, and not due to some other unaccounted factors.

For example, in one individual (patient #15) in the first retrospective study, the physician in charge believed that the renal transplant patient was intolerant of nifedipine XL in terms of its effect in controlling blood pressure. Upon switching the patient to amlodipine, his mean systolic blood pressure decreased by approximately 10 mmHg while his mean diastolic blood pressure was reduced by about 15 mmHg. Since the patient was only receiving monotherapy for the treatment of hypertension in both analysis periods, one can quite confidently say that the effect observed can, for the most part, be attributed to the antihypertensive effect of amlodipine. Because no other concomitant antihypertensive medications were given that may have differed in composition and dosage between the two analysis periods, this factor can be eliminated as a cause of the observed decrease in blood pressure with amlodipine therapy. However, other undetected or uncontrolled for confounding variables may have played a role in this marginal decrease in blood pressure.

Although the observed decrease in mean blood pressure of the two cohorts following amlodipine administration are statistically significant, this
reduction, in each individual cohort, as a whole, is not considered clinically significant. This holds particularly for the cohort examined in the first retrospective study where the mean reduction in blood pressure was in the order of 2 to 3 mmHg. The second cohort studied had a mean blood pressure decrease in the order of 6 mmHg which is more clinically significant than those obtained with the first cohort.

This observed difference in overall blood pressure reduction may be attributed to the design of the two retrospective studies. We modified the amlodipine analysis period in the second study by examining the antihypertensive effect of the drug at a later time (i.e., approximately at steady state). Such a modification of the amlodipine analysis period may explain the more pronounced decrease in overall blood pressure observed in this cohort.

Another possible explanation for the difference in observed mean reduction in blood pressure between the two cohorts may be due to the fact that the composition of the patients was more heterogeneous in the first cohort. Six patients in the first retrospective study were being treated for hypertension secondary to chronic renal failure. It has been mentioned earlier that the most difficult type of hypertension to treat is that associated with this condition.
For example, the 23rd patient of the second study had chronic renal failure and exhibited no blood pressure control while on amlodipine with an increase in both mean SBP and DBP of approximately 15 mm Hg. This change in blood pressure was more than likely due to a change in the status of the child’s disease than to the inability of amlodipine to lower blood pressure. In fact, the patient experienced an acute allograft rejection during amlodipine therapy. This marked change in blood pressure did not reflect the cohort’s blood pressure control, and likely affected the mean blood pressure during amlodipine therapy.

Since amlodipine provided equal, if not slightly improved blood pressure control in most of the pediatric patients studied, a physician may not be inclined to prescribe amlodipine to his/her patients in favour of another calcium channel blocker if only marginal blood pressure reduction can be achieved. However, amlodipine has advantages over other commercially available calcium channel blockers that make it particularly attractive in pediatric patients. These main advantages cited by pediatricians (The Hospital for Sick Children) for the use of amlodipine in the two patient cohorts examined included once daily dosing, and the availability of a liquid preparation, thus facilitating the administration of more individualized doses to
a child. This data was collected from the nurses notes and doctor’s orders form in each patient health chart.

Although not commercially available, such liquid formulations of amlodipine tablets are readily prepared at the Hospital for Sick Children as mentioned in the Methods section of the third study (page 48). This liquid preparation is ideal for younger children who require a long-acting calcium channel blocker to treat chronic hypertension, but are unable to swallow the large tablets commercially available (e.g. nifedipine XL, felodipine ER). These tablets must not be divided and must be swallowed intact since both extended-release formulations of nifedipine and felodipine have mechanisms designed within their coating which account for their long duration of action. These mechanisms act by delaying absorption of the pharmacologically active drug from the gastrointestinal tract.

One young bone marrow transplant patient examined in the second retrospective study (patient 1, Table IV), for example, required a long-acting calcium channel blocker to improve control of his high blood pressure but he was unable to swallow extended-release tablets of both nifedipine and felodipine. As a result, the patient was initially given a combination of a short-acting calcium channel blocker, two diuretics, and a vasodilator. When amlodipine was later administered as a liquid, the patient’s blood pressure was
then treated further with just one diuretic. Without the availability of a liquid preparation of a long-acting antihypertensive, treatment of this patient’s hypertension would depend on the use of multiple drugs and complex dosing schedules that are costly for the parent and inconvenient for the health care professional and the patient.

In addition, the available dosage forms of the extended-release calcium channel blockers and amlodipine may be too high for a given child’s size since these agents were designed and marketed for the adult population. In the case of the child discussed above the smallest available dose of amlodipine (2.5 mg) was considered too large to initiate therapy since the patient weighed only 11 kg. By preparing a liquid formulation it became possible to administer a clinically accepted dose volume of approximately 0.10 mg/kg/day and the patient was maintained on this daily dose.

As mentioned in the Introduction, single daily dose antihypertensive agents are preferred because they should provide smooth blood pressure control for 24 hours with minimal fluctuations in their blood pressure-lowering effect. Once daily dosing may also prove advantageous in the pediatric setting because it may improve a patient’s compliance. It has been demonstrated that compliance is inversely related to the number of pills a patient takes or the number of times a day the patient has to take medication149.
Furthermore, noncompliance has been identified as a serious problem in children who have undergone renal transplantation or who are treated with dialysis for conditions such as chronic renal failure. Such individuals are taking numerous medications chronically, and the introduction of a once-daily calcium channel blocker may improve their compliance\textsuperscript{150-152}. One should stress that although extended-release formulations of nifedipine and felodipine are usually given once a day, it was not uncommon to see these agents given twice a day to some of the individuals which were examined in the two cohorts. This contrasts the situation with amlodipine since this drug is always given once daily.

In the second retrospective study of bone marrow transplanted patients, it was observed that the number of antihypertensive medications received decreased in seven patients after amlodipine therapy was started. In six children, the number of medications remained constant in both periods of analysis, but increased in only two patients after the introduction of amlodipine. This reduction in the number of antihypertensive agents given to most of these children should improve their compliance. Because the patients presented in these two retrospective studies were hospitalized, compliance could not be assessed. However, it is of concern when the patient is at home.
Both retrospective studies differed in the adverse event profile observed during amlodipine therapy. In the first study, no adverse events were recorded that could be attributed to amlodipine since the event recorded (urticarial rash) was resolved despite the continuing of administration of the calcium channel blocker. In contrast, there was a single incidence of ankle edema (i.e. type of peripheral edema) in two patients in the bone marrow transplant cohort.

Peripheral edema is the most commonly reported adverse event associated with amlodipine and has an incidence of 5.6-8.5% in adult men and 14.6-15% in adult women\textsuperscript{153-156}. The adverse events of amlodipine have not been studied in children. However, it is possible that this adverse event was caused by amlodipine since the edema subsided a few days after the drug was discontinued. This form of edema related to amlodipine in adults does not appear to result from sodium or water retention and, as a result, usually fails to respond to diuretic treatment\textsuperscript{157} as was the case in the two study children.

The fact that both pediatric patients were withdrawn from amlodipine therapy shortly after the appearance of ankle edema is of clinical concern since it suggests that this adverse event may not be well tolerated by children. Alternatively, the withdrawal of amlodipine may merely reflect the lack of physician’s experience with this drug since he/she may have interpreted this relatively benign adverse effect in the context of other forms of edema.
In contrast to the situation in children, amlodipine appears to be well tolerated in adults since this calcium channel blocker is discontinued in less than 2% of patients due to the development of peripheral edema\textsuperscript{157}. However, an assessment of the safety and incidence of amlodipine in children cannot be made using the information in both retrospective studies since the sample size and assessment period are too small. The reporting of adverse effects is a major methodological issue in retrospective studies as it may reflect various degrees of quality of documentation by the medical staff.

Finally, the first retrospective study demonstrated that seven common serum laboratory constituents remained unchanged before and during amlodipine treatment. When changing from one pharmacological agent
to another, it is usually not desirable if the new drug drastically changes the values of these laboratory parameters unless the change is beneficial to the patient.

Part III:

In contrast to the two retrospective studies, there was no statistical difference in the overall blood pressure control (both 30 day home and 24-hour day and night SBP and DBP) between amlodipine and other long-acting calcium channel blockers (i.e. nifedipine/felodipine).

Although two individuals of our cohort refused to participate in 24-hour ambulatory blood pressure monitoring (ABPM), the results should have statistical merit since this form of evaluation of antihypertensive treatment has the advantage of allowing a researcher to use a reduced sample size in comparison to the sample size requirements of traditional methods of blood pressure measurement (e.g. twice-daily recordings)\textsuperscript{158}. The sample size requirements are smaller because the standard deviation of the difference between measurements is smaller during ABPM because of more repeated measurements during a given day.
ABPM is useful since blood pressure varies considerably during the day. In fact, blood pressure exhibits a circadian rhythm with a rise in the morning when a person has awaken (peak at 10 A.M), plateaus during the day, and then gradually decreases to its lowest value at around 3 A.M. Furthermore, it has been determined that the occurrence of cardiovascular events (e.g. stroke, myocardial infarction, and sudden cardiac death) also exhibit a similar circadian variation and these events occur more frequently during the morning after one has awaken.

Ambulatory blood pressure monitoring (ABPM) is a more useful clinical tool for predicting cardiovascular events associated with hypertension than other methods of measuring blood pressure. For instance, many studies have shown that there is a stronger correlation between target organ damage and ABPM than between intermittent clinic blood pressure monitoring and target organ damage.

Furthermore, the natural decline in nocturnal blood pressure is absent or less marked in some renal, heart and liver transplants. It has been postulated that control of nocturnal hypertension may help in decreasing target organ damage such as left ventricular hypertrophy.

It was demonstrated in the renal transplant cohort, as a whole, that amlodipine and nifedipine/felodipine did not differ in their control of nighttime
blood pressure; however, some individuals in this pediatric cohort had higher nocturnal than daytime blood pressure during the same drug treatment.

During amlodipine treatment one patient had a higher nighttime than daytime mean SBP, but with nifedipine therapy had both higher mean nocturnal SBP and DBP. Another patient had a higher mean nocturnal DBP during felodipine than during amlodipine therapy while this same parameter was higher in another individual during amlodipine treatment. Furthermore, one patient had both higher mean nighttime DBP readings during both amlodipine and nifedipine treatment.

In a clinical study by Lingens et. al.\textsuperscript{169}, which employed 24-hour ambulatory blood pressure monitoring in 34 pediatric renal transplant patients, 28 patients had nocturnal hypertension. Fourteen of these 28 patients were hypertensive at night but were normotensive during the day. There was also no difference in antihypertensive or immunosuppressant therapy or in renal function between those who were hypertensive only at night and those who were hypertensive during the entire 24 hours.

Our study provides evidence that nocturnal blood pressure elevation is very common in pediatric renal transplant patients and does not necessarily have to be accompanied by daytime hypertension. Furthermore, nighttime hypertension appears to be refractory to antihypertensive therapy in most cases.
Thus, it should not be surprising that some of the 11 renal transplant patients studied at the Hospital for Sick Children had higher nocturnal blood pressure despite using long-acting calcium channel blockers.

Compliance did not differ between the amlodipine and nifedipine/felodipine treatment periods. In fact, patient compliance (percentage of the drug taken by patient versus number of pills prescribed) was very high during both treatment periods in this pediatric cohort.

However, the high patient compliance observed on both arms of this study may be an artifact since the study investigator routinely contacted the families, and hence, there was an intervention here in terms of compliance. It is likely that without such intervention under normal everyday conditions, the advantage of a once-daily liquid preparation in improving patient compliance would be evident.

Although there was no evidence of improvement in compliance during amlodipine treatment when compared directly to other calcium channel blockers, the second retrospective study suggests that the addition of amlodipine to an antihypertensive regimen could improve a patient’s overall compliance, because the number of antihypertensive medications used decreased in about half the patients following the introduction of amlodipine.
I will now discuss some plausible explanations for the differing results obtained when both a retrospective and a prospective study were conducted to evaluate the efficacy of amlodipine.

First, the mean amlodipine dosages used in the first (initial dosage: 0.14 ± 0.01 mg/kg/day; maximum dosage: 0.22 ± 0.03 mg/kg/day) and second (initial dosage: 0.12 ± 0.01 mg/kg/day; maximum dosage: 0.16 ± 0.02 mg/kg/day) retrospective cohorts were larger than those used by the renal transplant patients in the prospective study (initial dosage: 0.09 ± 0.01 mg/kg/day; maximum dosage: 0.12 ± 0.02 mg/kg/day). Presumably, higher doses of amlodipine will provide a more pronounced antihypertensive effect. Using unpaired t-tests, a significant difference was observed between the first retrospective study and the prospective study in terms of mean initial and maximal amlodipine dosage (p = 0.02 and p = 0.04, respectively). However, there was no significant difference between the second retrospective study and the prospective study when the two parameters were compared (initial dosage: p = 0.15; maximal dosage: p = 0.14).

Secondly, the fact that the patients studied in the two retrospective studies were hospitalized, they likely had more bedrest than the outpatients of the prospective study. Cumulative bedrest is a factor that may explain the
observed decrease in mean blood pressure observed in the two retrospective studies.

In addition, the use of amlodipine during hospitalization had a temporal relationship associated with it since this calcium channel blocker was always introduced as a second drug after initial antihypertensive therapy. This temporal trend or "order effect" may, in part, explain the statistically significant reduction in blood pressure during amlodipine therapy that was demonstrated in the two retrospective studies, but was not observed in the prospective study.

For instance, it is possible that the hospitalized patients were displaying "white coat hypertension". White coat hypertension is a persistently elevated blood pressure measured in the hospital and a normal pressure at other times (e.g., at home). Many patients exhibit higher blood pressures when first hospitalized, but it frequently decreases over time due to environmental (e.g., habituation to the hospital setting) or statistical factors (e.g., regression to the mean). Furthermore, the medical condition for which each patient was hospitalized may have played a role in his/her elevated blood pressure at first, but as this condition was treated or resolved a reduction in blood pressure may have followed and coincided with amlodipine treatment, which was always given as second treatment.
In the case of the prospective study, the possibility of a temporal relationship affecting blood pressure was avoided since the study was conducted in a cross-over design involving randomization of treatment. In addition, there was little or no white-coat hypertension since the patients were primarily at home for the duration of the study.

Furthermore, a placebo effect may have played a role in blood pressure reduction when patients were given amlodipine during hospitalization. Presumably, the placebo effect cannot be discounted in the case of the prospective study because patients and their parents were encouraged to participate in the study based on the advantages amlodipine had over their current choice of calcium channel blocker. However, the use of ambulatory blood pressure monitoring in the prospective study gives the results obtained more credibility since it has been documented that this method of blood pressure measurement reduces the placebo effect\(^{170}\).

The discussion above cited specific examples of variables that were not easily controlled for when examining retrospective data. Such factors as “white coat hypertension” may have been responsible for the difference in blood pressure control observed between the retrospective studies and the prospective study.
Potential Advantages of the Retrospective Study Design

On the other hand, retrospective studies done properly have their merits as well. In comparison to prospective studies, retrospective studies usually cost less to conduct and take less time to complete as the data “collects themselves” (e.g. during compassionate use of amlopine in a series of single patients at our institution). These types of studies also allow one to extract, analyze, and draw conclusions on important data that would otherwise be ignored.

Hospital charts and databases contain useful data on such topics as drug treatments and surgical procedures. The use of retrospective hospital data as a source of information is particularly important in the field of pediatric drug treatment since children, as mentioned previously, have been almost universally excluded from most short and long-term pharmaceutically-sponsored clinical trials.

When a drug, such as amlodipine, is used clinically for the first time in children at the Hospital for Sick Children, it is, for the most part, reasonably monitored by the health care professionals to ensure that it has its desired effects. This is particularly important in the specific case of hypertensive transplant and nephrology patients since failure of pharmacological treatment for this condition may have serious repercussions with respect to the children’s
long-term health and survival. Thus, drug dosing and measurement of blood pressure is standardized and recording of such parameters is quite meticulous. As a result, conclusions drawn from this relatively accurate source of retrospective data have merit and can serve as an impetus for future prospective clinical pharmacological studies in the pediatric population.

Finally, the second retrospective study provided insightful information regarding the safety of amlodipine that was not observed in the prospective study. With this information on safety, pediatricians will be more often well-informed to deal with this possible safety issue (i.e., intolerance to ankle edema) when it becomes more widespread as amlodipine use increases in the pediatric population.

6. CONCLUSION:

Taking into consideration that there are confounding variables present when drawing conclusions from retrospective studies, both studies provided evidence that amlodipine is at least as effective as baseline treatment in controlling pediatric hypertension in transplant patients and individuals with underlying renal abnormalities. These conclusions were verified when a prospective study was conducted of renal transplant patients. In this study, amlodipine provided similar blood pressure control to nifedipine or felodipine.
when two distinct methods of measuring the blood pressure were applied. The prospective study also provided evidence that patient compliance during amlodipine was equal to that of other long-acting calcium channel blockers. Finally, all three studies demonstrated that short-term amlodipine therapy was generally tolerated by pediatric patients since there were very few adverse events reported. Since amlodipine is as effective as other once-daily calcium channel blockers in pediatric patients, it should become the drug of choice for treatment of hypertension in this population since it has unique properties which are advantageous to children. These properties include once daily dosing, and the availability of a liquid preparation of this calcium channel blocker allowing precise dosing and an ability to administer more appropriate dosages of the drug to pediatric patients.
7. REFERENCES


98. Triggle DJ, Janis RA. The 1,4-dihydropyridine receptor: a regulator component of the Ca\(^{2+}\) channel. Journal of Cardiovascular Pharmacology 1984: 6 (Suppl. 7): S949-S955.


8. APPENDICES

1. A paper summarizing the retrospective study of the efficacy and safety of amlodipine in pediatric bone marrow transplant patients has been accepted for publication in the scientific journal Clinical Pediatrics (Cleveland, Ohio) and is currently in press.

2. A paper summarizing the retrospective study of the efficacy and safety of amlodipine in pediatric transplant and nephrology patients has been submitted to the journal Pediatrics.

3. A paper has been submitted to the Journal of Pediatrics which summarizes the antihypertensive amlodipine in pediatric renal transplant patients.
Amlodipine Therapy for Hypertension in Pediatric Patients

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Abstract

Objective: Amlodipine is a new calcium channel blocker with potential for increased utility in children due to the unique physiochemical properties of water solubility and prolonged intrinsic half life permitting once-a-day administration. The drug has not been previously evaluated in children.

Study design: We retrospectively evaluated the first 23 children who either converted from another calcium channel blocker to amlodipine or had amlodipine added to their antihypertensive regimen in our institution.

Results: Amlodipine was at least as effective as standard antihypertensive therapy in maintaining target systolic and diastolic blood pressure. For both values, there were statistically lower pressures measured with amlodipine (after dose titration) as compared to the baseline (2.5 ± 1.1 mm Hg lower for systolic and 3.1 ± 1.5 mm Hg for diastolic, p < 0.05). No clinical or laboratory adverse effects were documented.

Conclusion: Amlodipine is safe and provides similar, if not slightly improved blood pressure control in children receiving pharmacological treatment for hypertension. Because of its prolonged elimination half life and the ability to give it in solution, amlodipine has advantages which should be considered by pediatricians treating children with hypertension.
Introduction

The pharmacological treatment of hypertension in children frequently includes a calcium channel blocker [1.2]. Therapeutic options are often limited in children by the impracticality of the commercially available calcium channel blocker formulations. Commonly, tablets and capsules are too large to be swallowed by children or the dosage forms available are excessive.

Amlodipine (Pfizer, Kirkland Quebec), a new dihydropyridine class calcium channel blocker, possesses unique physiochemical properties [3] which makes it potentially attractive for use in children. Unlike the extended release calcium channel blockers that prolong their blood pressure lowering effect by controlling the rate of drug absorption, and hence require the dose form to be ingested intact, the extended antihypertensive effect of amlodipine results from its slow elimination half life (e.g., $T_{1/2} \geq 30$ hours). The fact that amlodipine's extended action is not contingent upon an intact delivery system permits the tablet of amlodipine to be fractionated or dissolved into a liquid suspension prior to dosing. Despite these potential benefits, amlodipine has not been evaluated in children with hypertension.
In an attempt to evaluate the efficacy and safety of amlodipine in pediatric patients, we report our experience with children who were either converted from another calcium channel blocker to amlodipine or had amlodipine added to their antihypertensive therapy at The Hospital for Sick Children, Toronto, Canada.
Methods

Pharmacy records were reviewed to identify patients who received amlodipine between July 1993 and July 1995. For each patient the information gathered before and after the onset of amlodipine therapy included: age; diagnosis most likely related to the hypertension; reason for choosing amlodipine; temporally related adverse reactions; systolic blood pressure (SBP) and diastolic blood pressure (DBP) measurements obtained during hospitalization or in an outpatient clinic; concurrent medication and dosage: serum creatinine, hemoglobin, hematocrit, platelet count, leukocyte count, sodium, and potassium.

The mean SBP and DBP measurements for each analysis period, that is, before amlodipine and during amlodipine therapy (after dose titration) were used for comparison. To be included in the analysis, at least 3 separate blood pressure readings for each observation period were required. Statistical comparisons were performed using a Student’s paired t-test. Unless otherwise specified the data are presented as mean ± SEM.
Results

Patient Characteristics: (Table I)

Twenty three of the 28 patients identified by pharmacy records had sufficient blood pressure data before and during amlodipine therapy to be included in the analysis (21 patients for DBP). The median age was 7 years (range: 2 weeks to 17 years) and 16 were males. All patients were receiving antihypertensive medications prior to the initiation of amlodipine. Amlodipine was used as a substitute for other calcium channel blockers (i.e., nifedipine or felodipine) in 19 of the 23 cases and replaced hydralazine and enalapril in 1 patient each. In 2 cases amlodipine was added to a diuretic or β-blocker. The average amlodipine dose used to initiate therapy was 0.14 mg/kg (range, 0.05 to 0.24). Ten (43%) patients required an increase in the amlodipine dose resulting in a mean maximal dose of 0.22 mg/kg (range, 0.08 to 0.66).

Blood Pressure: (Table II)

The SBP and DBP were significantly lower during amlodipine therapy (after dose titration) compared with baseline (2.5 ± 1.1 mm Hg and 3.1 ± 1.5 mm Hg, respectively; p < 0.05). When the 3 patients with a clinically relevant decrease in the dose of prednisone ( >5 mg) or cyclosporine ( > 10% decrease from baseline) between the two observation periods were removed from the analysis.
the mean SBP and DBP decreased by 2.6 ± 1.3 mm Hg and 2.9 ± 1.7 mm Hg, respectively (p = 0.05 and 0.11).

Laboratory Data: (Table III)
There were no significant changes in serum sodium, potassium, creatinine, leukocyte count, platelet count, hemoglobin, or hematocrit with amlodipine therapy. There was a clinically nonsignificant downward trend in the leukocyte count and upward trend in the serum potassium.

Adverse Drug Reactions:
There were no adverse reactions temporally related to amlodipine therapy.

Discussion
This analysis demonstrated a slight lowering of the SBP and DBP in children with treated hypertension when the amlodipine was substituted for other antihypertensive medications or added to the antihypertensive regimen. The observed decrease in blood pressure during amlodipine may reflect uncontrolled difference between the observation periods such as blood pressure measurement technique.
the placebo effect, superior pharmacodynamic effect of amlodipine, improved ability to titrate the dose of amlodipine, or improved compliance with the once-a-day dosing of amlodipine solution. Included in the many factors which may effect blood pressure are the medications prednisone and cyclosporine. Although there was a downward trend in the SBP and DBP when the 3 patients with clinically relevant changes in cyclosporine or prednisone were excluded, the statistical significance was no longer present. The change in statistical significance most likely represents a limitation of our sample size and the clinically diminutive change in blood pressure rather than an effect of the medications themselves as the average decrease in SBP (1.5 mm Hg) and DBP (1.4 mm Hg) for the 3 excluded patients is less than the observed decrease for the study cohort (SBP: 2.5 mm Hg; DBP: 3.1 mm Hg).

In the majority of patients (83%) amlodipine was substituted for another calcium channel blocker. Availability of a liquid medication, ability to prescribe small doses, and once-a-day dosing were the predominant reasons given for the use of amlodipine.

Amlodipine is available in 2.5, 5 (scored), and 10 mg tablets. Although amlodipine is water soluble, an oral solution is not commercially available.
The current practice for preparing a liquid dose of amlodipine at the Hospital for Sick Children is to dissolve a 5 mg tablet in 5 mL of water using a dose container immediately prior to the dosing period. The appropriate dose is given using a syringe and the remainder is discarded. A new solution is prepared for each dose. There is no information available concerning the stability and efficacy of dissolved amlodipine. The typical dose, extrapolated from the weight adjusted adult dose, used to initiate amlodipine therapy is 0.10 to 0.15 mg/kg given once daily. The dose does not need to be adjusted for renal insufficiency [4] because the drug is mainly biotransformed to inactive metabolites.

Numerous reports in adult patients with hypertension have shown amlodipine to be safe and effective in the treatment of hypertension [5,6]. Although reported to occur less frequently, adverse effects of amlodipine are similar to those reported for other calcium channel blockers consisting of flushing, headaches, edema, and dizziness [5]. In a small percentage these adverse events were severe enough to warrant withdrawal of the drug. In our series of 23 patients there were no adverse events associated with amlodipine therapy. However, a single patient identified by the search of pharmacy records, but not included in the analysis because of insufficient data, developed a urticarial rash.
during amlodipine therapy which resolved despite the continuation of amlodipine. Similar to the adult experience, there were no significant changes in the laboratory values reviewed.

We conclude that amlodipine is safe and provides similar, if not slightly improved blood pressure control in children receiving pharmacological treatment for hypertension.
References


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* discontinued with amlodipine therapy; Nif, nifedipine; SA, short-acting; PA, prolonged action; XL, extended release; HCTZ, hydrochlorothiazide; ECMO, extracorporeal membrane oxygenation; BPD, bronchopulmonary dysplasia; AHUS, atypical hemolytic uremic syndrome
**Table II: Blood Pressure (mean ± SEM)**

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<th>During Amlodipine</th>
<th>p-value</th>
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<td></td>
<td>(mm Hg)</td>
<td>(mm Hg)</td>
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<td><strong>All Patients</strong></td>
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<td>SBP (23)</td>
<td>126.7 ± 2.9</td>
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<td>DBP (21)</td>
<td>80.2 ± 2.4</td>
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<td><strong>Patients with consistent Pred and CSA dose</strong></td>
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<td>SBP (20)</td>
<td>125.8 ± 2.9</td>
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<td>DBP (18)</td>
<td>80.7 ± 2.6</td>
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Table III: Serum Laboratory Values (Mean ± SEM)

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<td>Sodium (mmol/L)</td>
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<td>137 ± 0.6</td>
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<td>Potassium (mmol/L)</td>
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<td>8.1 ± 1.0</td>
<td>&gt; 0.05</td>
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<tr>
<td>Platelets (10^9/L)</td>
<td>282 ± 45.8</td>
<td>280 ± 40.4</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>Hemoglobin (g/L)</td>
<td>109 ± 4.1</td>
<td>106 ± 3.9</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>Hematocrit (%)</td>
<td>33 ± 1.3</td>
<td>32 ± 1.2</td>
<td>&gt; 0.05</td>
</tr>
</tbody>
</table>

WBC, white blood cells (leukocytes)
The Efficacy of Amlodipine in Pediatric Bone Marrow Transplant Patients

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Key words: amlodipine, bone marrow transplant, blood pressure

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Abstract

The calcium antagonist amlodipine may have the potential for expanded use in children due to its physiochemistry and pharmacokinetic profile that facilitates once-daily dosing in a liquid formulation. Its safety and efficacy have not been previously evaluated in children. A retrospective analysis of 15 pediatric bone marrow transplant patients who had amlodipine incorporated into their antihypertensive drug regimen reveal significantly lower blood pressure as compared to baseline therapy [123.5 ± 2.1 mmHg and 117.2 ± 2.2 mmHg (systolic blood pressure before and during amlodipine; p< 0.05); 81.5 ± 1.8 mmHg and 75.5 ± 2.6 mmHg (diastolic blood pressure before and during amlodipine; p< 0.05)]. Amlodipine provided improved blood pressure control in this cohort and may provide a valuable pharmacological alternative for treatment of pediatric hypertension.
Introduction

In children hypertension may commonly arise from pathophysiological processes affecting the renovascular, renal parenchymal, cardiovascular and endocrine systems or may be drug-induced. This contrasts the situation in adults where the etiology of this disease is usually unknown\textsuperscript{1-4}. In bone marrow transplant patients, the potent immunosuppressant agent cyclosporine used for graft-versus-host disease prophylaxis and treatment is associated with an increased prevalence of hypertension. Hypertension develops shortly after initiation of cyclosporine therapy and its incidence can be further increased by the addition of corticosteroids to immunosuppressant therapy\textsuperscript{5-6}.

Calcium antagonists are commonly administered to treat hypertension in children, whether as monotherapy or in combination with other pharmacological agents. However, the commercially available calcium antagonist formulations in use (e.g. nifedipine, felodipine) are designed for adults and their use is limited in the pediatric population. Typically, tablets or capsules of such antihypertensives are too large to be swallowed by young pediatric patients and/or the dosage sizes available may be too excessive for a given child’s size.

Amlodipine is a relatively new calcium antagonist of the dihydropyridine class which possesses unique physiochemical properties of prolonged intrinsic elimination half-life and water solubility which set it apart from other dihydropyridine-based antagonists, and may offer advantages to pediatric patients. These unique properties facilitate once-daily dosing in a liquid preparation. The objective of this study was to describe the efficacy of amlodipine in children, by analysing our institutional experience with pediatric patients who were administered amlodipine as part of their pharmacological treatment for hypertension secondary to bone marrow transplantation.
Methods

Fifteen pediatric bone marrow transplant patients who were treated with amlodipine were identified by hospital pharmacy records. Patient chart reviews were performed and the period of analysis of antihypertensive therapy ranged from May 1994 to June 1996 and encompassed periods before and during amlodipine treatment. All identified bone marrow transplant patients were administered amlodipine at some point during the aforementioned period of analysis. The following information was extracted for each patient: gender; age; weight; diagnosis responsible for bone marrow transplant; indications for amlodipine; types and doses of medications given before and during amlodipine therapy; systolic blood pressure (SBP) and diastolic blood pressure (DBP) measurements; and adverse events recorded during amlodipine treatment.

The mean SBP and DBP measurements of each patient were used for comparison of efficacy of the two treatment periods; before and during amlodipine therapy. The length of the analysis period prior to amlodipine treatment was confined to the 3 days prior to the initiation of amlodipine since this was likely the period when the patient was hypertensive and the physician was deciding to substitute amlodipine for another blood pressure lowering agent or to incorporate this calcium antagonist into the antihypertensive regimen. The amlodipine treatment analysis period was set from the fifth day and on from the commencement of amlodipine therapy since it typically takes approximately five half lives for steady state levels of the medication to be reached in the circulation and hence a maximal effect on blood pressure to be encountered.

Blood pressure measurements were obtained in our institution by various bone marrow transplant ward nurses using a Dinamap monitor with a Dura cuff (Medicare Inc.) or a Hewlett Packard electrocardiogram unit with calibrated V-Lok cuffs (W.A. Baum Co., Inc. U.S.A.) Typically, blood pressure measurements are recorded six times per day. Manual blood pressure measurements with a Tycos sphygmomanometer were used on occasion to confirm the accuracy of a given measurement. The nurses were not blinded to the antihypertensive medications each patient received. The data in the results are presented as mean ± SEM. and statistical comparisons of blood pressure before and during amlodipine therapy were conducted using Student’s paired t-tests.
Results

Patient Characteristics:

The median age for our patient cohort was 8 years (range: 1 to 17 years) and 9 were females. All patients were administered amlodipine orally once daily. Four of the younger patients received amlodipine in the form of a liquid preparation in an attempt to match the dose to their weight. The average initial dose of amlodipine used in antihypertensive therapy was 0.12 mg/kg/day with a mean maximum dose of 0.16 mg/kg/day (Table 1). The recommended initial dosage of amlodipine for adults is 0.10 mg/kg/day. Four patients had their amlodipine dosage increased while one patient was given a loading dose twice the corresponding maintenance doses. The percentage increase in amlodipine dose and frequency of dose changes varied in each of the four patients and was based on a clinical decision by the specific hematologist/oncologist in charge of each patient.

In the majority of our patients, the onset of hypertension was following transplantation while one patient diagnosed with neuroblastoma experienced hypertension prior to receiving a bone marrow transplant.

Blood Pressure:

Eleven of the fifteen patients (73%) had an overall individual reduction in both systolic and diastolic blood pressure after amlodipine therapy was initiated. Both the SBP and DBP were significantly lower in our patient cohort during amlodipine therapy when compared with baseline therapy (6.5 ± 2.7 mmHg and 5.9 ± 2.7 mmHg, respectively; p< 0.05) [Table 2].

Adverse Drug Events:

Two patients experienced ankle edema during amlodipine which led to discontinuation of the drug in both cases.

Discussion

Our retrospective analysis demonstrated both statistically and clinically significant reductions of both SBP and DBP in children undergoing
pharmacological treatment for hypertension when amlodipine replaced one or more antihypertensive medications or was added to an existing antihypertensive regimen. Since this is a retrospective study the apparent difference in blood pressure may reflect also a placebo effect, uncontrolled changes in variables between the two analysis periods, or an error due to our limited sample size.

In a few of the 11 patients that experienced a overall decrease in blood pressure the reduction was minimal. In two patients (#11, #15) with normal blood pressure, amlodipine replaced a single antihypertensive agent which was administered more than once-a-day. This practice is very common in our institution so as to provide a more convenient dosing schedule for our patients and it helps to improve compliance. However, this cohort, as a whole, had a significant reduction in blood pressure during amlodipine therapy as compared to the analysis period prior to the introduction of this calcium antagonist.

One problem which we identified was the variation in the magnitude and frequency of amlodipine dose changes ordered by various staff pediatricians. In a few children, the amlodipine was increased several times without allowing this calcium antagonist to reach steady state concentrations at a given dose. We suggest in the future that pediatricians take the pharmacokinetic properties of amlodipine into account and only increase the dose of this agent if blood pressure control is insufficient after approximately one week. Two patients (#9, #14) in our cohort that experienced an increase in mean blood pressure during amlodipine were subject to this dosing dilemma. This oversight may have hindered a proper assessment of the ability of amlodipine to control each patient’s blood pressure.

The main advantages of amlodipine included the availability of a liquid formulation, an improved ability to administer more appropriate doses to the child, and once-daily dosing. These properties of amlodipine result from physiochemical properties that are not possessed by other dihydropyridine calcium antagonists. Firstly, the amlodipine molecule exists primarily in an ionized form at physiological pH^7 and has high water solubility. As a result, amlodipine can be converted into a liquid by dissolving the tablet dose in water. Although there is no commercially available liquid formulation of amlodipine our institution’s pharmacy provides a dissolvant dose container so that a liquid preparation of the drug can easily be created. This liquid preparation is administered to children who cannot swallow other calcium antagonist capsules and tablets (eg. extended-release nifedipine) or is used to optimize a child’s dose.
Furthermore, in adults, amlodipine's intrinsic elimination half-life (53 ± 14 hours)\(^8\) is significantly prolonged when compared to other calcium antagonists\(^9\). This profile allows for once-daily dosing in children and results in smooth daily blood pressure control without major fluctuations in peak-trough concentrations\(^10\). In contrast to amlodipine, the extended-release calcium antagonists (e.g., nifedipine, felodipine) provide once-daily dosing and prolonged blood pressure reduction via a mechanical control of the rate of absorption which relies on an intact delivery system. As a result, the available dosage forms of such drugs cannot be broken down to tailor it for a child's weight specifications.

In the specific case when amlodipine replaces a calcium antagonist administered more than once-daily (e.g., nifedipine PA), the switch may improve long term patient compliance. It has been demonstrated that compliance is inversely related to the number of pills taken by the patient\(^11\). Although compliance is not an issue in our patient sample because they were all hospitalized while receiving their blood pressure medications, it is an area of concern when the patient is at home.

Upon initiation of amodipine therapy, it was found that the number of antihypertensive medications decreased in 7 patients when compared to the antihypertensive regimen prior to amlodipine. In 6 individuals, the number of medications remained constant in both analysis periods and only increased in 2 patients during amlodipine treatment.

Numerous studies in adults have shown amlodipine to be as effective and safe as monotherapy in the management of patients with mild to moderate severe hypertension\(^12-15\). Furthermore, adult clinical trials have demonstrated that amlodipine is effective and generally safe when used in combination with other antihypertensive drugs. Amlodipine potentiates the efficacy of diuretics\(^16\), \(\beta\)-blockers\(^17-18\), ACE inhibitors\(^19,20\) and other calcium antagonists\(^21\).

The adverse event profile of amlodipine in adults is similar to that of other calcium antagonists\(^22-24\). However, in studies where the dosages were titrated to provide therapeutically equivalent reductions in blood pressure, it was found that there were less withdrawals of amlodipine therapy due to adverse events compared to nifedipine PA\(^10\), nitrendipine\(^25\), and felodipine\(^26\).
In adults, edema represents the highest overall incidence of side effects with amlodipine but is mild in nature and rarely warrants drug cessation. Specifically, there was a 9.8% incidence of ankle edema during amlodipine therapy in an adult sample investigated by Osterloh et al. Ankle edema was observed during amlodipine therapy in our study. However, we could not make any conclusions about the incidence of this adverse event in children due to our small sample size.

In conclusion, in pediatric bone marrow patients amlodipine provides equal if not better blood pressure control when it is added to a antihypertensive regimen or used as replacement therapy for treatment of hypertension. Amlodipine may be better suited for pediatric treatment of hypertension than existing calcium antagonist therapy because of once-daily dosing, the ability to administer more individualized doses, and the option of administering a liquid preparation. A future prospective study comparing the efficacy and safety of amlodipine to standard antihypertensive treatment would be useful to control for some of the confounding variables present in this study and is currently in progress at our institution.
Table I: Characteristics of Pediatric Bone Marrow Transplant Patients

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<tr>
<th>Patient Number</th>
<th>Gender</th>
<th>Age (Yrs)</th>
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<th>Amlodipine Dose (mg/kg/day)</th>
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<td>M</td>
<td>1</td>
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Table 2: Mean Patient Blood Pressure Before and During Amlodipine Therapy

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<th>Patient Number</th>
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<tr>
<td>Mean</td>
<td>123.5 ± 2.1</td>
<td>117.2 ± 2.2</td>
<td>81.5 ± 1.8</td>
<td>75.5 ± 2.6</td>
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SBP= Systolic Blood Pressure  
DBP= Diastolic Blood Pressure
Bibliography


THE EFFECTIVENESS OF AMLODIPINE IN PEDIATRIC HYPERTENSION; A RANDOMIZED PROSPECTIVE, CROSSOVER TRIAL

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ABSTRACT:

A prospective study in a crossover design was conducted at the Hospital for Sick Children on 11 nephrology patients (10 had received renal transplants) to compare the efficacy and compliance of amlodipine to that of other long-acting calcium channel blockers (i.e. felodipine or nifedipine). Utilizing Student’s paired t-tests, no significant difference was observed in mean systolic blood pressure (SBP) and diastolic blood pressure (DBP) between each 30 day calcium channel blocker treatment ($p = 0.09$, $p = 0.27$, respectively). It was also demonstrated using 24-hour blood pressure monitoring that there was no significant difference between each drug treatment period in both mean day time ($p = 0.78$) and nighttime SBP ($p = 0.96$), and also in mean day time ($p = 0.65$) and nighttime DBP ($p = 0.95$). Furthermore, patient compliance was similar in both the amlodipine and the nifedipine/felodipine treatment period ($p = 0.94$). This data suggests that amlodipine provides comparitively effective monthly and 24-hour blood pressure control in pediatric nephrology patients as that of other long-acting calcium channel blockers. However, amlodipine may be ideally suited for treatment of pediatric hypertension since it is the only calcium channel blocker which can be administered once-daily as a liquid preparation.
INTRODUCTION:

The incidence of pediatric hypertension has been estimated at between 0.8% and 9%\textsuperscript{1,2} and this disease has been attributed to underlying renal parenchymal abnormalities in 70% of the cases in a study of children under 10 years of age\textsuperscript{3}.

Hypertension is a frequent complication in renal transplant patients\textsuperscript{4} and may be caused by multiple factors which include intact native kidneys, renal artery stenosis, acute and chronic rejection, recurrence of the original renal disease, and drugs (eg. cyclosporine and corticosteroids)\textsuperscript{5,6}.

Post-transplantation hypertension is a serious clinical problem since there is evidence that it is associated with a significant decrease in allograft survival\textsuperscript{7-9} and the disease is the most important risk factor for cardiovascular morbidity and mortality in transplant patients\textsuperscript{10}. Hypertension following renal transplantation appears to be more common in children than adults\textsuperscript{11}.

Since the introduction of cyclosporine as an immunosuppressant, the incidence of hypertension following renal transplantation has risen from a range of 45% to 50% to a range of 67% to 86%\textsuperscript{12-19}. Furthermore, the nature of pharmacological treatment for this disease has changed following the use of this immunosuppressant agent since the renin-angiotensin system appears now to play a minor role in the pathogenesis of hypertension\textsuperscript{20}. Cyclosporine causes afferent
arteriolar vasoconstriction and this is believed by many to be the primary mechanism by which this agent causes hypertension\textsuperscript{21,22}.

Calcium channel blockers are considered an ideal first-line agent for the treatment of post-transplantation hypertension\textsuperscript{23-25} since they can partially counteract the renal vasoconstrictive effects of cyclosporine\textsuperscript{26-32} and have been shown and postulated to mediate renal protection through various mechanisms\textsuperscript{33}.

Calcium channel blockers are used frequently in hypertensive children since there are relatively low rates of adverse effects at low to moderate doses but there is insufficient information describing the efficacy and long-term safety of these antihypertensive agents\textsuperscript{34}. Amlodipine is a relatively new dihydropyridine-based calcium channel blocker which may be ideal for first-line treatment of pediatric post-transplantation hypertension since it can be administered once-daily as a liquid preparation. Since there is no data on the efficacy of amlodipine in children, a comparative prospective study of pediatric renal transplant patients was conducted by us to address this issue.

**METHODS:**

**Patients**

Eleven patients between nine and seventeen years of age who were receiving a calcium channel blocker (i.e. nifedipine or felodipine) for treatment of
hypertension were recruited from the nephrology outpatient clinic at our institution. Ten of the patients had previously received a renal transplant. Patients were included in the study if their transplant occurred at least three months prior to their recruitment and they exhibited stable blood pressure control (i.e. no changes in dosage and type of antihypertensive therapy) one month before recruitment. Patients were excluded if they had a known allergy to calcium channel blockers. The study protocol was approved by our institution’s research ethics board.

**Drug Treatment**

In a randomized crossover design, each patient received amlodipine and nifedipine (or felodipine) in two separate 30 day treatment periods. For example, if the patient was randomized to receive nifedipine in the first treatment period, he/she would receive amlodipine in the second treatment period. There was no washout period between treatment periods for ethical reasons. Amlodipine was administered as an oral suspension once-daily at an approximate initial dose of 0.10 mg/kg. The maximum initial dose permitted was 5mg. If the patient’s blood pressure was not in the normotensive range (i.e. below the 95th percentile for age and gender) following one week of therapy, the staff nephrologist raised the dosage by 50% to 100% to a maximum of 10 mg. The primary investigator was blinded to any changes in dosage. The dosage of either nifedipine or felodipine
given as tablets was unchanged during the study and was previously titrated by the
staff nephrologist prior to the study so that the patient’s blood pressure was in the
normotensive range for age and gender.

Blood Pressure Measurement

Blood pressure was monitored twice daily at home by an adult caregiver
using either a mercury sphygmomanometer or an automated oscillometric device
(Critikon Inc., Tampa Fla.). The caregivers were trained by the staff nephrology
nurses to obtain blood pressure measurements using a standardized technique and
appropriate blood pressure cuff size (4 from thesis 2nd Task Force). The patient
had blood pressure recorded using the same arm while in the supine position.
Ambulatory blood pressure was recorded over a 24 hour period during the last
week of each treatment period using a Takeda blood pressure monitor model TM
2420 (A & D Engineering Inc., California) or an ambulatory blood pressure
monitor model 90207 (Spacelabs Medical, Mississauga, Ontario). Each monitor
was preset to measure blood pressure every half hour during the day (9 A.M. to 10
P.M.) and each hour during the night (10 P.M. to 9 A.M.).

Compliance

Compliance was assessed using the Medication Event Monitoring System
(MEMS, Aprex, California). The MEMS® Trackcap™ is a medication bottle
cap which contains microelectronic a microelectronic tracking device. The
electronic chip in the lid of the cap recorded the date and time a medication bottle containing each study drug treatment was opened by the patient. The parents and child were unaware of the purpose of this electronic monitoring device.

**Adverse Effects**

Patients were instructed to record any adverse events which may have occurred during each 30 day treatment period.

**Statistical Analysis**

With mean diastolic blood pressure as a primary endpoint, a sample of eleven patients was sufficient to show a median effect size difference in blood pressure between the two drugs with an alpha of 0.05 and a power of 80%. An effect considered clinically significant was any value greater than 10 mm Hg. Amlodipine was compared to nifedipine and felodipine with respect to: mean 30 day systolic blood pressure (SBP) and diastolic blood pressure (DBP), mean 24 hour SBP and DBP during both the day and night, and the rate of compliance (percentage of drug taken versus prescribed amount). All comparisons were performed using a Student’s paired t-test. Data are presented as mean ± SEM.
RESULTS:

Pediatric Patient Characteristics (Table I):

The median age of the cohort was 16 years (range: 9 to 17) and included six males and five females. The mean initial dose of amlodipine used to initiate therapy was 0.09 ± 0.01 mg/kg/day. Four patients required an increase in amlodipine dosage so that the mean maximal amlodipine dose was 0.12 mg/kg/day. Six patients were treated with a single calcium blocker throughout the study while the remaining individuals had combination therapy for treatment of their hypertension. The additional antihypertensive agents used by these five patients were not of the calcium channel blocker class and their dosages were identical in each treatment phase of the study.

Blood Pressure Control:

1. Mean 30 Day Blood Pressure (Table II):

There was no significant difference in both the cohort’s mean 30 day SBP and DBP when comparing the two treatment periods. Eight patients had an individual mean reduction in SBP during amlodipine therapy while six patients experienced a lower mean DBP during this treatment period.
2. Mean 24 Hour Blood Pressure:

a) Day time:

No significant difference was evident in cohort mean day time SBP (amlodipine: 126.6 ± 3.4; nifedipine\felodipine: 127.5 ± 3.4; p = 0.78) and DBP (amlodipine: 78.6 ± 2.2; nifedipine\felodipine: 77.5 ± 2.2; p = 0.65).

b) Nighttime:

No significant difference was found between each drug treatment period in both cohort mean nighttime SBP (amlodipine: 119.5 ± 2.9; nifedipine\felodipine: 119.3 ± 3.3; p = 0.96) and DBP (amlodipine: 74.7 ± 3.2; nifedipine\felodipine: 74.5 ± 3.4; p = 0.95).

Compliance:

There was no significant difference in mean compliance (i.e. percentage of drug taken versus prescribed amount) between the amlodipine (93.4 ± 1.7) and the nifedipine\felodipine (93.4 ± 1.6) treatment periods (p = 0.94).

Adverse Effects:

No adverse effects were recorded by any patients during either drug treatment period.
<table>
<thead>
<tr>
<th>Patient Number</th>
<th>Age (Yrs)</th>
<th>Gender</th>
<th>Weight (kg)</th>
<th>Renal Diagnosis</th>
<th>Amlodipine Dosage (mg/kg/day) Initial/Max</th>
<th>Ca²⁺ Channel Blocker Therapy Prior to Amlodipine</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>9</td>
<td>F</td>
<td>35</td>
<td>Focal Segmental Glomerulosclerosis</td>
<td>0.07/0.07</td>
<td>Nifedipine PA 20 mg o.d.</td>
</tr>
<tr>
<td>2</td>
<td>10</td>
<td>M</td>
<td>27</td>
<td>Autosomal Dominant Polycystic Kidney Disease</td>
<td>0.10/0.10</td>
<td>Nifedipine XL 30 mg o.d.</td>
</tr>
<tr>
<td>3</td>
<td>12</td>
<td>M</td>
<td>30</td>
<td>Renal Dysplasia</td>
<td>0.07/0.07</td>
<td>Nifedipine XL 30 mg o.d.</td>
</tr>
<tr>
<td>4</td>
<td>14</td>
<td>M</td>
<td>37</td>
<td>Cystinosis</td>
<td>0.07/0.07</td>
<td>Felodipine E.R 15 mg o.d</td>
</tr>
<tr>
<td>5</td>
<td>16</td>
<td>M</td>
<td>45</td>
<td>Cystinosis</td>
<td>0.11/0.11</td>
<td>Felodipine E.R. 10 mg o.d</td>
</tr>
<tr>
<td>6</td>
<td>16</td>
<td>F</td>
<td>46</td>
<td>Radiation-induced Nephritis</td>
<td>0.11/0.22</td>
<td>Nifedipine XL 30 mg b.i.d.</td>
</tr>
<tr>
<td>7</td>
<td>16</td>
<td>M</td>
<td>72</td>
<td>Alport’s Syndrome</td>
<td>0.07/0.10</td>
<td>Nifedipine XL 30 mg b.i.d.</td>
</tr>
<tr>
<td>8</td>
<td>16</td>
<td>F</td>
<td>90</td>
<td>Unknown</td>
<td>0.06/0.11</td>
<td>Nifedipine XL 60 mg o.d.</td>
</tr>
<tr>
<td>9</td>
<td>17</td>
<td>F</td>
<td>34</td>
<td>Bilateral Wilms Tumour</td>
<td>0.15/0.22</td>
<td>Felodipine ER 10 mg b.i.d.</td>
</tr>
<tr>
<td>10</td>
<td>17</td>
<td>F</td>
<td>35</td>
<td>Adult Polycystic Kidney Disease</td>
<td>0.14/0.14</td>
<td>Nifedipine XL 30 mg o.d.</td>
</tr>
<tr>
<td>11</td>
<td>17</td>
<td>M</td>
<td>60</td>
<td>Nephrotic Syndrome</td>
<td>0.08/0.08</td>
<td>Nifedipine XL 30 mg o.d.</td>
</tr>
</tbody>
</table>
Table II: Patient Mean Home 30-day Blood Pressure

<table>
<thead>
<tr>
<th>Patient Number</th>
<th>S.B.P. During Nifedipine/Felodipine (mm Hg)</th>
<th>S.B.P. During Amlodipine (mm Hg)</th>
<th>D.B.P. During Nifedipine/Felodipine (mm Hg)</th>
<th>D.B.P. During Amlodipine (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>122.8</td>
<td>113.2</td>
<td>74.4</td>
<td>65.8</td>
</tr>
<tr>
<td>2</td>
<td>104.7</td>
<td>105.4</td>
<td>73.3</td>
<td>74.9</td>
</tr>
<tr>
<td>3</td>
<td>113.8</td>
<td>115.6</td>
<td>82</td>
<td>83.8</td>
</tr>
<tr>
<td>4</td>
<td>116.4</td>
<td>114.9</td>
<td>79.8</td>
<td>79.2</td>
</tr>
<tr>
<td>5</td>
<td>114.4</td>
<td>112.8</td>
<td>78</td>
<td>79.7</td>
</tr>
<tr>
<td>6</td>
<td>134</td>
<td>131.6</td>
<td>78.9</td>
<td>81.7</td>
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<tr>
<td>7</td>
<td>136.3</td>
<td>136.1</td>
<td>79.2</td>
<td>73.2</td>
</tr>
<tr>
<td>8</td>
<td>128.3</td>
<td>123</td>
<td>89.3</td>
<td>86.2</td>
</tr>
<tr>
<td>9</td>
<td>127.9</td>
<td>123.9</td>
<td>83.9</td>
<td>79.1</td>
</tr>
<tr>
<td>10</td>
<td>119</td>
<td>121.6</td>
<td>74.8</td>
<td>74.6</td>
</tr>
<tr>
<td>11</td>
<td>115.9</td>
<td>114.3</td>
<td>74.8</td>
<td>75.7</td>
</tr>
</tbody>
</table>

Mean 121.2 ± 3.0* 119.3 ± 2.6* 79.0 ± 1.7** 77.6 ± 1.3**

* p-value = 0.09 (Student’s paired t-test)

** p-value = 0.27 (Student’s paired t-test)
DISCUSSION:

This study demonstrated that amlodipine provides as effective monthly and 24 hour blood pressure control as that of other long-acting calcium channel blockers in pediatric renal transplant patients. These findings are supported by adult data which demonstrated that amlodipine is effective in treatment for hypertension following renal transplantation.35

However, amlodipine has advantages over other long-acting calcium channel blockers which make this agent particularly suitable for the treatment of pediatric hypertension. First, amlodipine has a relatively long intrinsic half-life of elimination (36 to 48 hours)36 which permits once-daily dosing for 24 hour blood pressure control. Other commercially available once-daily calcium channel blockers (e.g. nifedipine, felodipine) provide similar blood pressure control artificially as extended-release formulations. Their long duration of action depends on an intact delivery system of the available tablet formulations. Unfortunately, younger children have had trouble ingesting these large tablets. Furthermore, the dosage forms of these extended-release calcium channel blockers were designed for adults and may be too excessive for a child’s size.

Amlodipine has a unique physio-chemical structure which sets it apart from other dihydropyridine-based calcium channel blockers. Amlodipine is water
soluble since it contains a terminal basic amino group (pK_2 = 8.6) which is 94% ionized at physiological pH^{37}. Although a liquid formulation of amlodipine is not commercially available, a liquid preparation of this drug can be readily created at our institution by dissolving a tablet dose in water using a dissolvant dose container.

Thus, amlodipine can be administered as a liquid to children who cannot swallow extended-release formulations of other calcium channel blockers and the doses given can be more individualized.

Although our study demonstrated that patient compliance during amlodipine therapy was similar to that of other long-acting calcium channel blockers, this may be an artifact since there was continuous intervention by the study investigators throughout the study to ensure compliance. It would be expected that superior patient compliance with amlodipine would be observed under normal circumstances without such intervention. This line of reasoning is justified by the demonstration in adults of comparitively better compliance to amlodipine therapy compared to other long-acting calcium channel blockers^{38,39}.

In addition, it is not uncommon for pediatric renal transplant patients to take extended release formulations of long-acting calcium channel blockers more than once-daily (e.g. patient # 6, # 7, # 9, Table 1) which contrasts the situation in amlodipine since this agent is always administered once-daily. It has been
documented that compliance is inversely related to the number of pills taken by patients\textsuperscript{40}.

In conclusion, this study indicates that amlodipine is an effective first-line agent for the treatment of hypertension following renal transplantation in pediatric patients and this agent has advantages over other long-acting calcium channel blockers which make it ideal for treatment of this disease in children.
REFERENCES:


