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Amlodipine Use in Pediatric Hypertension

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Since its release in 1992, amlodipine, a vasoselective dihydropyridine calcium channel blocker, has become a frequent component of antihypertensive regimens in adults. It offers several potential advantages compared to other agents in this class, including once daily dosing, few significant drug interactions, and a relatively mild adverse effect profile. Although there have been only a small number of studies to document its efficacy in children, many pediatric institutions are now using amlodipine as a primary therapy for managing hypertension.

Mechanism of Action

Like all calcium channel blockers, amlodipine inhibits the movement of calcium ions across cell membranes. It acts primarily via inhibition of the influx of calcium into vascular smooth muscle and, to a lesser extent, cardiac muscle. As a result, amlodipine produces peripheral arterial vasodilation and lowers blood pressure, with relatively little negative inotropic effect. Amlodipine interacts with calcium ion channels by an ongoing association/dissociation with the receptor binding site, producing a gradual onset of action.[1-3]

Clinical Use in Children

A small number of publications are available describing the use of amlodipine in infants and children.[4-10] In 1998, Pfammatter and colleagues studied the effects of amlodipine in 28 children between 3 and 19 years of age.[4] Fifteen patients had underlying renal disease, eight had post-renal transplant hypertension, three had essential hypertension, one child had Prune-belly syndrome, and one had a coarctation of the abdominal aorta. The children were treated with standard adult doses of 5 to 10 mg once daily, producing a weight-based dose of 0.19-0.3 mg/kg/day. Amlodipine was withdrawn in five patients because of edema and flushing. In the remaining patients, amlodipine produced a significant reduction in blood pressure during the 12 week observation period, with an average decrease in systolic blood pressure of 21 mm Hg and diastolic blood pressure of 12 mm Hg. Heart rate and body weight were unchanged. The authors concluded that amlodipine was effective in the treatment of hypertension in their sample population.

Also that year, a retrospective evaluation was conducted in 15 children (ages 1 to 17 years) receiving amlodipine for hypertension following bone marrow transplantation.[5] The average initial dose in this population was 0.12 mg/kg/day (given once daily), with an average maximum dose of 0.16 mg/kg/day. In six of the patients, amlodipine was successful as monotherapy. Overall, amlodipine produced a significant reduction in blood pressure, with an average decline in systolic blood pressure of 6.5$\pm$2.7 mm Hg and diastolic blood pressure of 5.9$\pm$2.7 mm Hg. Two patients experienced edema which required discontinuation of therapy.

In 1999, Tallian and colleagues conducted a prospective, open-label study of once-daily amlodipine in 21 children (mean age 13.1 years).[6] Sixteen children had essential hypertension, and five had hypertension associated with renal disease. The average starting dose was 0.07$\pm$0.04 mg/kg/day. Doses were titrated to achieve blood pressure values below the 95th percentile for age and gender. The mean effective dose after titration was 0.29$\pm$0.11 mg/kg/day in the children less than 13 years of age, compared to 0.16$\pm$0.11 mg/kg/day for the older patients. There was no difference in dose based on the cause of hypertension. Fourteen of the 16 patients with essential hypertension achieved target blood pressures with amlodipine as monotherapy.

Silverstein and colleagues compared amlodipine with nifedipine in a cross-over study of 24 pediatric renal transplant recipients.[7] The authors found no significant differences between

the two drugs in blood pressure response, effect on cyclosporine concentrations, or glomerular filtration rates. The incidence of adverse effects was higher during treatment with nifedipine. Of note, 22 patients developed gingival hyperplasia during nifedipine use. All experienced stabilization or reduction of this adverse effect when switched to amlodipine.

In 2000, Rogan and colleagues conducted a second prospective comparison trial of amlodipine in children.[8] Eleven children (9 to 17 years of age) with hypertension who were already receiving either felodipine or nifedipine were enrolled in this crossover study. The two treatment arms consisted of the patient's current regimen and amlodipine, with each arm lasting for 30 days. The mean initial amlodipine dose was 0.09 mg/kg/day. Four patients required a dose escalation, resulting in a mean maximal dose of 0.12 mg/kg/day. Six patients received their calcium channel blocker as monotherapy, while the remaining patients required additional antihypertensives.

There were no significant differences in blood pressure measurements with the two treatments. Mean daytime systolic blood pressures were 126.6±3.4 mm Hg for amlodipine and 127.5±3.4 mm Hg for nifedipine/felodipine. Mean daytime diastolic values were 78.6±2.2 mm Hg for amlodipine and 77.5±2.2 mm Hg for nifedipine/felodipine. Nighttime measurements were also similar. There were no differences between the groups in compliance or adverse effects. The authors concluded that amlodipine was as effective as standard calcium channel blockers in their pediatric population and offered the advantage of once-daily dosing.

In 2000, Flynn, Smoyer, and Bunchman performed a retrospective review of 55 children and adolescents in their practice treated with amlodipine between 1996 and 1999.[9] The mean age of the patients was 11.5±5.4 years (range 13 months to 20 years). In 58% of the patients, amlodipine was the initial medication chosen; while in the remaining patients, amlodipine was added to other antihypertensive therapies. Amlodipine produced a significant reduction in blood pressure. Systolic blood pressure decreased from 129±12 mm Hg at baseline to 122±12 mm Hg after treatment, and diastolic blood pressure decreased from 78±13 mm Hg to 70±19 mm Hg.

The authors found a significant inverse relationship between patient age and effective dose in their patient population. The youngest patients (0 to 6 years of age) required an average dose of 0.30±0.16 mg/kg/day, compared to 0.16±0.12 mg/kg/day for children 6 to 12 years of age and 0.14±0.10 mg/kg/day for those 12 to 20 years of age. More of the younger children also required twice daily dosing to achieve blood pressure control. The authors concluded that amlodipine was an effective agent for children with hypertension, and that younger children appeared to require higher doses to achieve optimal blood pressure control.

A case series from University Children's Hospital in Switzerland published the following year adds further support for the efficacy of amlodipine in children.[10] In this series, 43 children ranging in age from 1.1 to 19 years (median 9.8 years) were treated for a 16 week observation period. All had chronic renal disease. At 16 weeks, the median decrease in blood pressure was 17/10 mm Hg. No changes in heart rate, weight, serum creatinine or electrolytes were noted.

Pharmacokinetics

After oral administration, amlodipine is well absorbed, with a bioavailability of 64 to 90%. Absorption is not affected by administration with food. Peak serum concentrations are reached in 6 to 12 hours following oral dosing. Amlodipine is widely distributed, with a volume of distribution of 16 to 21 L/kg, and is highly protein bound (approximately 93%). It is extensively metabolized by the liver to inactive metabolites. Elimination is bi-phasic, with a terminal half-life of 30 to 50 hours in adults. Total body clearance is approximately 0.4 L/hr/kg. Patients with hepatic dysfunction may have a delayed clearance of drug. Doses should be reduced in these patients to account for this delay. No dosage adjustment is necessary for patients with renal dysfunction.[1-3]

In a 2002 abstract, Flynn and colleagues described the pharmacokinetic parameters of amlodipine in children.[11] In this multicenter trial, 74 children between 6 months and 17 years of age previously receiving amlodipine were enrolled. The mean dose at the time of the study was 0.17±0.13 mg/kg/day (range 0.03 to 0.77 mg/kg/day). Eighty-two percent of the children were receiving amlodipine as a once daily dose. At the median weight (45 kg), the estimated volume of distribution was 25.1 L/kg. The rate of clearance was 23.7 L/hr for males and 17.6 L/hr for females. The authors concluded that pharmacokinetic parameters in children receiving amlodipine were not significantly different than those in adults and were not influenced by frequency of dosing, suggesting that once-daily administration was appropriate.

Adverse Effects

Amlodipine is well tolerated by most patients. In clinical trials in adults, the rate of discontinuation (1.5%) was no different than that of placebo. The most commonly reported adverse effects were headache (in 7.3% of patients), edema (1.8 to 10.8%), dizziness (1.1 to 3.4%), flushing (0.7 to 2.7%), and palpitations (0.7 to 4.5%). Other adverse effects reported in 1 to 4% of patients receiving either amlodipine or placebo include: fatigue, nausea, abdominal pain, somnolence, muscle cramps, pruritus, and rash. The incidence of hypotension, arrhythmias, and peripheral ischemia with amlodipine use was less than 1%. In post-marketing surveillance, gynecomastia and hepatic dysfunction (with jaundice and elevated hepatic transaminases) have been reported.[1-3]

In pediatric reports, amlodipine has been associated with the development of edema, fatigue, flushing, headache, dizziness, and nausea.[4-10] In the study by Tallian and colleagues, two patients experienced chest pain that resolved with a 50% reduction in amlodipine dose.[6] A mild increase in heart rate was also noted in the paper by Flynn et al.[9] The average heart rate for the 55 children increased from 91±19 to 98±25 beats per minute during the study period. The authors felt this effect was not clinically significant. In addition to these study results, a case of telangiectasia and gingival hyperplasia in a 3 year old girl receiving amlodipine was recently reported.[12] The patient had been on therapy for approximately one year because of hypertension which developed after hemolytic uremic syndrome. Both symptoms had progressively worsened over the year, but resolved with discontinuation of amlodipine.

Drug Interactions

In contrast to most of the other calcium channel blockers, amlodipine has few significant drug interactions. Studies of amlodipine administration with other common cardiac medications, as well as other highly protein bound drugs such as digoxin, phenytoin, and warfarin, have failed to produce clinically significant effects. Patients receiving concomitant therapy with drugs that induce cytochrome P450 3A4 (such as rifampin) or inhibit this enzyme (amprenavir, indinavir, quinupristin/dalfopristin, and azole antifungals) should be monitored for a potential change in amlodipine response.[1-3]

Availability

Amlodipine (Norvasc®; Pfizer) is available in 2.5, 5, and 10 mg tablets.[2] Extemporaneous formulations have been developed to prepare a 1 mg/ml suspension using either 1% methylcellulose or a mixture of commercially available suspending agents (OraSweet® and OraPlus®).[13]

Dosing Recommendations

The usual starting dose for amlodipine in adults is 5 mg given once daily. Patients with hepatic insufficiency should be initially treated with half this dose. A maximum daily dose of 10 mg is recommended by the manufacturer.[1,2]

Based on the studies available to date, amlodipine should be initiated in children at a dose of 0.05 to 0.1 mg/kg/day given once daily. The dose may be increased as needed to achieve blood pressure control. In most of the pediatric patients studied, doses of 0.2 to 0.25 mg/kg/day were required for optimal response. Younger children appear to require higher doses, often as much as 0.3 to 0.4 mg/kg/day. Titration should be done slowly, at one to two week intervals, to fully assess response.[4-8]

Summary

Based on preliminary work, amlodipine appears to be an effective treatment for hypertension in children. It offers the advantages of once daily dosing, few significant drug interactions, and a generally mild adverse effect profile. In addition, the ability to prepare an extemporaneous oral liquid formulation makes it a feasible alternative for young children. More research is needed to compare it to other standard antihypertensive therapies in children and to assess its long-term adverse effect profile.

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Pharmacology Literature Review

Bosentan Use in Children

An open-label efficacy, safety, and pharmacokinetic study of bosentan was conducted in 19 children with pulmonary artery hypertension. For 4 weeks, patients received bosentan dosed according to weight (31.25 mg in patients 10-20 kg, 62.5 mg in patients 20-40 kg, and 125 mg in patients > 40 kg). After 4 weeks, the dose was titrated to optimal response and then continued for an additional 8 weeks. Pharmacokinetic variables were similar to data previously published for adults. Bosentan produced hemodynamic improvement, with a mean reduction in pulmonary artery pressure of 8 mm Hg and a reduction in pulmonary vascular resistance index of 300 dyne·s·m^2/cm^5. Barts RJ, Ivy D, Dingemanse J, et al. Pharmacokinetics, safety, and efficacy of bosentan in pediatric patients with pulmonary artery hypertension. **Clin Pharmacol Ther 2003;73:372-82.**

Inhaled Corticosteroids

This review addresses the devices used for administration of inhaled corticosteroids, methods for assessing the effectiveness of these delivery systems, and the impact of changing propellants on drug deposition. The author highlights the benefits of the newer devices (eg, improved drug delivery), but also warns of the potential for greater systemic drug absorption and adverse effects. Newman SP. Deposition and effects of inhaled corticosteroids. **Clin Pharmacokinet 2003;42:529-44.**

Nicardipine Use During ECMO

The authors of this case describe the use of a nicardipine infusion for the management of hypertension in a neonate during extracorporeal membrane oxygenation (ECMO). Nicardipine was initiated at a rate of 0.5 mcg/kg/min and titrated to 1.5 mcg/kg/min during the two day treatment period. Although no specific pharmacokinetic/pharmacodynamic information on nicardipine in ECMO is available, the authors suggest that higher doses may be necessary because of the larger circulating blood volume and loss within the circuit. McBride BF, White CM, Campbell M, et al. Nicardipine to control neonatal hypertension during extracorporeal membrane oxygen support. **Ann Pharmacother 2003;37:667-70.**

Octreotide for Chylothorax

Several recent case reports have documented the efficacy of octreotide for the management of chylothorax. In this paper, a 5 month old baby who developed chylothorax five days after an atrioventricular canal repair is presented. Intravenous octreotide was initiated at 3.5 mcg/kg/hr and continued for 4 days. Chylous drainage decreased from 7.14 ml/hr prior to initiation of octreotide to 0.83 ml/hr. In addition to their case, the authors review the literature on this use for octreotide. Al-Zubairy SA, Al-Jazain AS. Octreotide as a therapeutic option for management of chylothorax. **Ann Pharmacother 2003;37:679-82.**

Once-daily Gentamicin for Neonates

Using a Bayesian approach and serum concentration data from 139 neonates, the authors of this paper created a model and algorithm for a new once-daily gentamicin dosing strategy. Based on their analysis, they recommend a daily gentamicin dose equal to (0.441+[0.0945 x gestational age]). While this dosing strategy would simplify empiric therapy, the authors acknowledge that additional clinical validation is needed. DiCenzo R, Forrest A, Slish JC, et al. A gentamicin pharmacokinetic population model and once-daily dosing algorithm for neonates. **Pharmacotherapy 2003;23:585-91**.

Formulary Update

The following actions were taken by the Pharmacy and Therapeutics Committee at their meeting on 6/27/03:

1. Bortezomib (Velcade®) was added to the Formulary as a third line therapy for multiple myeloma.
2. The restriction on bivalirudin (Angiomax®) was amended to include use in patients undergoing percutaneous coronary intervention.

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