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PHARMACOLOGY REVIEW

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Calcium channel blockers: pharmacology and place in therapy of pediatric hypertension

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Abstract The calcium channel blockers (CCBs) are a diverse group of antihypertensive medications with variable pharmacokinetics and clinical effects. Although CCBs have been widely applied to the treatment of hypertensive children, data regarding the pharmacokinetics, efficacy and safety of these agents in children are extremely limited. In this review we briefly summarize the mechanism of action of CCBs and then summarize pertinent pharmacokinetic information on each of the CCBs commonly used in children, including amlodipine, diltiazem, felodipine, isradipine, intravenous nicardipine, nifedipine and verapamil. Clinically important drug interactions and adverse effects are discussed, as well as the potential role of CCBs in renal protection. Available pediatric efficacy and safety data are summarized, and recommendations made regarding the rational use of CCBs in the management of pediatric hypertension.

Key words Calcium channel blockers · Children · Pharmacokinetics · Hypertension

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Introduction

In recent years, several new classes of antihypertensive agents have found increasing use in the treatment of pediatric hypertension, most notably calcium channel blocking agents (CCBs) and angiotensin converting enzyme inhibitors. Despite the paucity of specific pediatric data regarding the safety and efficacy of these drugs in children, drugs from these classes have supplanted older agents such as diuretics and beta-blockers as first-line therapy of pediatric hypertension, not only in clinical practice, but also in published recommendations regarding the treatment of childhood hypertension [1–3]. In this review, we will summarize pertinent pharmacologic and therapeutic aspects of CCBs, including pediatric data where available, and examine the potential role of these agents in the therapy of pediatric hypertension.

Location, structure and function of calcium channels

Calcium plays an essential role in many cellular processes throughout the body, and preservation of normal function of many types of cells depends on the maintenance of a calcium concentration gradient across cell membranes, with the extracellular calcium concentration being approximately 10,000 times greater than the intracellular concentration. This concentration gradient is particularly important for contraction and relaxation of vascular smooth muscle (VSM) cells [4–7]. Among the mechanisms utilized by VSM and other cells to maintain this concentration gradient, calcium channels located on the cell membrane play a key role.

Numerous classes and subclasses of calcium channels have been described (Table 1), with the major type of importance with respect to hypertension being the L-type, or "long-acting," voltage-sensitive calcium channel [7–12]. L-type channels are widely distributed in the cardiovascular system, especially in the myocardium and VSM, and are the target of all CCBs currently in clinical

Table 1 Voltage-sensitive calcium channel subtypes (adapted from refs. [7, 11, 12, 15, 16, 21])

Type	Voltage	Distribution	Major functions	Blocked by
L (long-acting)	High	Predominantly myocardium and smooth muscle	Muscular contraction	Verapamil, diltiazem and dihydropyridine CCBs
N (neuronal)	High	Presynaptic nerve terminals	Catecholamine release	ω-Conotoxin GVIA
P (Purkinje)	High	Presynaptic nerve terminals, mainly in cerebellar Purkinje neurons	Neurotransmitter release	Agatoxin FTX
Q	High	Presynaptic nerve terminals	Neurotransmitter release	Agatoxin FTX
R	High	Neural tissue	Neurotransmitter release	Cadmium
T (transient)	Low	Postsynaptic nerve terminals and nodal tissue (sinoatrial, atrioventricular)	Pacemaker activity	Mifebradil[a]

[a] Withdrawn from market

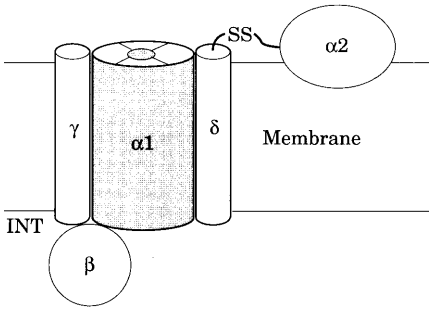

Fig. 1 Subunit composition of the L-type calcium channel. See text for descriptions of subunits. (Reprinted by permission from ref. [12])

use. Of the other types of calcium channels, only the T-type channel has been found to have clinical importance with respect to hypertension and other cardiovascular disease [5, 9, 13]. For a discussion of the other types of calcium channels, the reader is encouraged to consult one of the several recent reviews on this topic [14–16].

The structure of the voltage-sensitive calcium channel has been described in detail [4, 9–12, 17]. As illustrated in Fig. 1, it is composed of several components, including the ion-conducting α_1-subunit, as well as several accessory subunits designated α_2, β, δ and γ. These subunits have all been sequenced and their genes identified [8–12]. The α_1-subunit is the most important component of the calcium channel, containing the "pore" through which calcium ions pass, and is the binding site of all of the CCBs currently in use. Variations in the α_1-subunit account for the differences in voltage and pharmacologic sensitivity between the voltage-sensitive channel types listed in Table 1 [10, 12]. The α_1-subunit itself contains several different functional regions to which the CCBs bind, with CCBs of different classes (see below) binding to different regions [7, 12, 17]. The α_2-, β,-, δ- and γ-subunits primarily act to modulate the function of the α_1-subunit [12, 18]. Regulation of the entire calcium channel itself is a function of neurotransmitters and other hormones, primarily via second messengers such as G-proteins [9].

Given the large extracellular-to-intracellular concentration gradient noted above, calcium will naturally tend to enter the cell whenever a calcium channel opens. Depolarization of the cell membrane causes a conformational change in the calcium channel that allows extracellular calcium to enter the cell. In the case of VSM cells, once calcium has entered the cell, a further release of calcium from the sarcoplasmic reticulum occurs, leading to activation of the actin-myosin complex and muscular contraction [4, 5, 7]. Regulation of this process occurs through a variety of mechanisms as noted above, and has been discussed elsewhere [9, 19]. The affinity of CCBs for their binding sites increases during membrane depolarization; thus, these agents prevent VSM cell contraction by interfering with calcium influx following depolarization. This same mechanism produces the myocardial depression and negative inotropic actions of the first generation CCBs, most notably verapamil. This effect is much less likely to be seen with the second and third generation dihydropyridine CCBs because of their increased vascular selectivity (see below), which makes them well suited to the treatment of hypertension.

The other major factor that may account for the efficacy of CCBs in the treatment of hypertension is an alteration in VSM calcium homeostasis [4, 20, 21]. Although a detailed discussion of this topic is beyond the scope of this review, several alterations in intracellular VSM calcium metabolism have been described in animal models of hypertension, including increased calcium uptake, decreased sodium-calcium exchange, and an increased intracellular calcium content [20]. This last phenomenon has a human parallel in the increased intracellular calcium content of platelets from hypertensive subjects. While the relationship of such experimental findings to the pathogenesis of human hypertension remains unclear at this time, it is possible that such abnormalities of calcium metabolism could lead to a state of increased peripheral vascular resistance [20, 21]. If true, this mechanism would provide a logical foundation for the incorporation of CCBs into antihypertensive regimens.

Pharmacologic classification of CCBs

Since the introduction of the CCBs onto the drug market, several classification schemes have been proposed. The oldest and one of the most widely accepted classifications is based upon the drugs' chemical structures. According to this scheme, CCBs are divided into benzothiazepines, phenylalkylamines, and dihydropyridines, exemplified by diltiazem, verapamil and nifedipine, respectively [22]. (A fourth class, the tetraols, has been developed, but the only agent in this class is mifebradil, which has been withdrawn from the market because of drug interactions.) Another classification scheme, that of Fleckenstein, divided CCBs into three groups, A, B, and C, with groups A and B being inhibitors of calcium-dependent excitation-contraction coupling, and group C having less specific, less potent effects on excitation-contraction coupling [23, 24]. Once the various calcium channel subtypes were identified (Table 1), CCBs were then classified as either "selective" or "non-selective," with the "selective" agents acting on the L-type slow channels, and the "nonselective" agents acting on the L, T, N, and P channels. Most recently, Toyo-Oka and Nayler have identified three generations of CCBs based on receptor binding properties, tissue selectivity, and pharmacokinetic profiles [22, 25, 26]. Nifedipine, diltiazem, and verapamil represent the first generation. The second generation includes agents with increased vascular selectivity, including isradipine and felodipine. Third generation agents, most notably amlodipine, are characterized by being highly lipophilic, and have high affinity for specific binding sites on the calcium channel, properties which are responsible for their gradual onset of action and prolonged duration of antihypertensive effect. This is perhaps the most useful classification of these agents, and is the scheme followed in this review.

Pharmacokinetics

As we have mentioned previously, the amount of pediatric data available regarding the therapeutic use of CCBs is extremely limited. The amount of pharmacokinetic data is even more limited, a problem that will need to be addressed in the future when new drugs are studied and marketed. Most of the data in this section will be adult data that we will attempt to extrapolate for pediatric purposes. Pertinent pharmacologic parameters are summarized in Table 2. (Authors' note: in this section of the review, CCBs of interest are reviewed in alphabetical order.)

Amlodipine

As will be seen from the following discussion, most calcium channel blockers, notably the dihydropyridine analogues, characteristically have low bioavailability [10–30%] and short elimination half-lives [3–6 h]. Amlodipine, however, is pharmacologically distinct from the rest of the group [27, 28]. The drug was designed in an effort to make a compound that produced typical dihydropyridine effects in vivo, but that would also exhibit an increased absolute bioavailability and prolonged duration of effect. Thus, amlodipine has an absolute bioavailability of 60–65%, with food having little effect on absorption. It has an extremely high tissue affinity and protein binding of approximately 97%, contributing to its large volume of distribution of 21 l/kg. Mean peak serum levels are linear and age independent: 3 ng/ml after 5 mg and 5.9 ng/ml after 10 mg oral doses in elderly or young healthy volunteers respectively [27, 28]. Its prolonged duration of effect can be explained by its extremely long elimination half-life, approximately 36 h in healthy volunteers, which can increase to as long as 45 h after repeated administration [28]. Its lipophilic character also leads to concentration of the drug in the lipid bilayers of the cell membrane, leading to a depot effect that results in sustained release of the drug to its site of action, the calcium channel [29, 30]. As noted below, these properties make amlodipine better suited for chronic antihypertensive therapy, as opposed to treatment of acute hypertension.

Amlodipine undergoes extensive hepatic metabolism, as do all CCBs. Amlodipine is oxidized to the pyridine analogue, with subsequent oxidative deamination of the 2-aminoethoxymethyl side chain or deesterification at the 5-methoxycarbonyl group. Several metabolites are produced by the breakdown of amlodipine, all of which are inactive and have no pharmacologic or therapeutic

Table 2 Pharmacokinetic parameters of selected CCBs. All data based on adult studies (*IR* immediate release, *ER* extended release)

Drug	Onset of clinical effect	Elimination half-life	Effect of renal insufficiency
Amlodipine	6 h	35–48 h	No significant effect
Diltiazem	30 min (IR)	3.2–6.6 h (IR), 5–10 h (ER)	No significant effect
Felodipine	2–5 h	10–16 h	Increased plasma concentrations of inactive metabolites
Isradipine	1 h	5–10.7 h	Increased bioavailability in mild renal insufficiency; decreased bioavailability in severe renal insufficiency
Nicardipine (IV)	1 min	8.6–14.4 h[a]	Decreased clearance in moderate renal insufficiency
Nifedipine	20 min (IR), 2–2.5 h (ER)	1.7–3.4 h (IR), 3.7–4.3 h (ER)	No significant effect
Verapamil	18 min (IR)	2-7 h (IR), 6.4–12 h (ER)	Decreased clearance in renal insufficiency

[a] Although nicardipine has a relatively long elimination half-life, when using the intravenous form, plasma concentrations will decrease by up to 50% within 2 h following discontinuation of the infusion

activity. The rate of oxidation of amlodipine may be slower than that of other CCBs as suggested by its less extensive first-pass metabolism and longer elimination half-life [31]. The drug undergoes approximately 60% renal excretion and 5–10% appears as unchanged drug in the urine. Another notable source of excretion is via the feces at 20–25%. Because of its hepatic metabolism, amlodipine concentrations in renal failure do not seem to increase to the point of clinical significance (Table 2), and the dosage usually does not need adjustment or supplementation during dialysis. However, as with many CCBs, adjustment may be warranted if the patient has extensive hepatic impairment.

Unfortunately, the studies that have been published on amlodipine use in children have primarily focused on efficacy and safety [32–36]. While several of these studies have suggested pharmacokinetic differences in children compared to adults, including a need to dose the drug twice daily to achieve adequate blood pressure control (see below), there is still a need for formal pharmacokinetic studies of this drug in children.

Diltiazem

Diltiazem is a benzothiazepine derivative that in addition to its effects on the VSM calcium channel also antagonizes the slow channels located in the cell membrane of cardiac muscle cells. Therefore, its primary indications are cardiovascular, encompassing angina, hypertension and arrhythmias. Diltiazem is commercially available in several different dosage forms, including immediate release tablets, extended release tablets, sustained release capsules and an intravenous form. The onset for immediate-release tablets is 30 min, with a peak response reached in 3–4 h [37]. Time to peak concentration is approximately 2–4 h, producing an area under the curve (AUC) of 535–685 ng/h/ml after a 90-mg immediate-release dose. The extended-release product reaches peak response in 3–6 h and peak concentration in 6–11 h [38]. Both the extended-release tablets and sustained-release capsules must be swallowed whole in order to achieve a sustained antihypertensive effect. Bioavailability of diltiazem is approximately 35–40% and is not greatly affected by food [39]. Diltiazem is 77–93% protein bound, with 35–40% being bound to albumin [40, 41]. The drug is extensively hepatically metabolized, with elimination half-lives of 3.2–6.6 h and 5–10 h for the immediate-release and extended-release formulations, respectively [37]. The pharmacokinetics of diltiazem is unaffected by renal insufficiency, but both bioavailability and elimination half-life are increased in patients with cirrhosis [38]. As discussed below, intravenous diltiazem is primarily indicated for the treatment of arrhythmias [42], so its kinetics will not be discussed in this review.

Felodipine

Felodipine is only available as an extended release product that has an initial onset of action of 2–5 h, with a peak response of 2–4 h. Mean peak serum concentrations are 4–6 nmol/l. These concentrations produced 50% of the maximum antihypertensive effect [43]. A correlation exists between plasma concentrations and blood pressure effects in healthy and hypertensive subjects. Other effects, including those on total peripheral resistance and forearm blood flow, are also dependent on plasma concentrations. However, the diuretic/natriuretic effects of felodipine seem to be dose dependent. Doses above 20 mg have been found to reduce both natriuresis and diuresis, while doses less than 20 mg seem to promote these effects [44]. Some investigators have targeted achieving plasma serum concentrations of 40 nmol/l, although plasma concentrations above 30 nmol/l may contribute to toxicity.

Similar to amlodipine, felodipine exhibits high tissue and protein binding of approximately 99%. An interesting property is that it also binds to some extent to erythrocytes, contributing to approximately 30% of the total plasma concentration [45]. The volume of distribution ranges from 6 to 18.2 l/kg. A three-compartment model best describes the distribution of felodipine. An initial, rapid distribution phase with a half-life of 6.4 min represents distribution into total body water. This is followed by a second, slower, distribution phase with a half-life of 1.6 h representing tissue reequilibration [46].

Felodipine, although completely absorbed from the gastrointestinal tract, only has an absolute bioavailability of about 15–20%. This is the result of extensive first-pass metabolism rather than poor absorption. Drug absorption may also be affected by administration with meals or grapefruit juice, as discussed later. The major route of metabolism is the oxidation of felodipine to the corresponding inactive purine analog [H152/37] via the cytochrome P450–3A pathway. Then H152/37 is further metabolized by cleavage of the methyl and ethyl ester groups and by oxidation of the methyl groups of the pyridine structure to corresponding alcohols [46]. These lead to the ten known felodipine metabolites, none of which has significant antihypertensive effects. The elimination half-life of the active compound is 10–16 h, enabling the drug to be dosed once daily. Metabolites of felodipine are excreted in the urine as both free acids and as conjugates that account for 37% of the excreted amount of the drug. Metabolites formed by aliphatic hydroxylation are excreted by first-order processes while the mono-acids decline in a biphasic manner. Levels of these metabolites may increase in renal failure (Table 2). Felodipine is also excreted minimally [10%] in feces. It is probably unnecessary to make dose adjustments for renal failure [45]. Only about 9% of felodipine is removed by dialysis, so supplemental doses are not needed.

One study of felodipine kinetics in children has been reported to date by Blowey et al. [47]. Six patients (aged 9.4–16.1 years) were studied, five of whom were also receiving cyclosporine A. Kinetic parameters reported were median t_{max} of 3.8 h, total plasma clearance of 79.8 ml/min×kg^{-1}, AUC of 747 nmol/l/h, and terminal half-life of 21.2 h. It should be noted that patient 6, the

only child not receiving cyclosporine A, had a markedly shorter terminal half-life of 7.2 h and a significantly lower AUC of 280 nmol/l/h [47]. The values from this patient may better reflect the expected values for a pediatric patient with isolated hypertension.

Isradipine

Isradipine is available as an immediate-release or extended-release product. Isradipine is rapidly and almost completely absorbed from the gastrointestinal tract after single dose oral administration. However, due to extensive first-pass metabolism, the estimated bioavailability of orally administered isradipine is just 14–24%. Bioavailability is unaffected by administration with food but may be altered in renal insufficiency (Table 2). The initial response to isradipine occurs in approximately 1 h, producing a peak response in 2–3 h [48]. The duration of action in adults is normally 12 h; however, full therapeutic response is usually not seen until the 2nd week of therapy. After administering 2.5–10 mg isradipine to normal subjects, the maximum plasma concentrations were 2.1–8.39 ng/ml, respectively. Peak plasma concentration is usually reached in 1.3–3 h after administration of the immediate release product [49, 50].

Similar to the previous two agents, isradipine exhibits high protein binding of 95–97.4%. It is bound predominately to α_1-acid glycoprotein, serum albumin and lipoproteins and binding is independent of pH. Isradipine undergoes hepatic metabolism via the P450 system involving deesterification and aromatization of the dihydropyridine moiety to yield pharmacologically inactive pyridine and carboxylic acid derivatives [51]. None of the metabolites has any therapeutic effect. The volume of distribution ranges from 69 to 191 l. Isradipine exhibits a biphasic elimination half-life, producing an alpha half-life of 1–2 h and a terminal half-life of 8 h [48]. Renal excretion accounts for 60–65% of elimination, and the drug is not dialyzed to any appreciable extent. There is no need for dose adjustment in patients with renal failure, or for supplementation in dialysis patients. The pediatric studies reported to date [52, 53] on the use of this drug have not included kinetic data.

Nicardipine

Given the absence of reports of oral nicardipine use in children, in this review we will only discuss the intravenous formulation. Based on adult data, the initial onset of nicardipine given intravenously occurs within 1 min, producing a reduction of 30% in mean arterial blood pressure and a 13–26% increase in heart rate [54, 55]. The duration of action after a single intravenous dose is approximately 3 h. Approximately 95% of nicardipine is bound by serum proteins, specifically α_1-acid glycoproteins (AAG), albumin, and lipoproteins. Like felodipine, nicardipine also binds to erythrocytes. The binding of nicardipine to albumin, AAG, and lipoproteins is extremely pH dependent. If the serum pH increases, so does the fraction of non-ionized or free nicardipine. Therefore protein binding also increases due to the increased availability of free nicardipine (eventually reaching saturation). This increase in binding affinity has been related to a change in the conformation of albumin (the neutral-base transition) which occurs in this pH range [56]. The increase in binding is related to a displacement of the ionization equilibrium favoring the lipid-soluble form of nicardipine. Changes in the serum concentration of AAG and albumin have been noted in patients with certain disease states, such as cancer, inflammation and sepsis. These patients characteristically have increased levels of AAG and decreased amounts of albumin, which may lead to alterations in nicardipine pharmacokinetics in patients with these conditions. However, it is probably unnecessary to automatically adjust the dose of nicardipine when treating such patients; its rapid onset of effect means that the dose can be easily and quickly titrated to the desired clinical response no matter what the underlying condition.

Following infusion, nicardipine plasma concentrations decline triexponentially, with a rapid early distribution phase (half-life of 2.7 min), an intermediate phase (half-life of 44.8 min), and a terminal phase (half-life of 14.4 h) that can only be detected after long-term infusions. The elimination half-life in adults is 8.6 h on average [57]. We would expect this to be much shorter in a pediatric patient; however, there are no pediatric pharmacokinetic data at this time to prove or disprove this assumption. The volume of distribution is approximately 8.3 l/kg. Rapid dose-related increases in nicardipine plasma concentrations are seen during the first 2 h after initiation of an infusion. The concentrations reach steady state at approximately 24–48 h. Upon termination of the infusion, plasma concentrations rapidly decline, with at least a 50% decrease during the first 2 h [57]. Nicardipine undergoes extensive hepatic metabolism via the P450 pathway. Transformation of the *N*-benzyl sidechain position 3 is the primary site of breakdown. Oxidation to the pyridine analog is also another source of metabolism. The principal metabolic routes would seem to be the major urinary alcohol metabolites S14 and S16 excreted as glucuronides [56]. Virtually no unchanged drug is found in the urine. Although nicardipine is principally metabolized by the liver, lower clearance has been reported in patients with renal impairment [57], so it is probably prudent to be more conservative in using the drug in such patients. Obviously the dose should be adjusted in severe hepatic impairment.

Nifedipine

Currently nifedipine is available both as an immediate-release and as an extended-release product. Bioavailability is similar for both formulations, approximately 52–56% [58]. The immediate-release product if used

should be taken without food due to possible reduced peak plasma concentrations and prolonged drug action time when administered with meals. The extended-release product, however, is not affected by food, and can be taken without respect to meals. The initial response after an immediate-release dose occurs in 20 min, with duration of 4–8 h. Peak concentration is reached in 20–45 min [59]. With the extended-release product, a biphasic peak concentration occurs related to the release of drug from the tablet matrix. The first peak occurs at 2–2.5 h, which produces the highest plasma concentration, then the second, lower peak follows 6–12 h after the dose was administered [60]. The reported duration of the extended-release tablet is approximately 24 h; however, more frequent dosing has been reported in pediatric patients [61, 62]. The explanation for this is unknown and is deserving of further study.

Nifedipine is 90–96% protein bound, which is decreased slightly [92–93%] in renal or hepatic impairment [63]. Interestingly, nifedipine is also extensively distributed to the placenta, and placental transfer occurs in some patients. The elimination half-life for the immediate release capsules is 1.7–3.4 h, for the biphasic extended-release tablet 3.7–4.3 h. Nifedipine undergoes significant hepatic metabolism via the cytochrome P450 (CYP) 3A4 enzyme system, with the majority oxidized to a free acid and a smaller fraction converted to a lactone. Twenty to 30% of the drug is removed from the portal blood supply by the liver due to first-pass metabolism. Intestinal wall metabolism also contributes greatly to the first-pass effect. Greater than 90% of a dose of nifedipine is excreted in the urine as inactive metabolites, with most urinary excretion occurring within the first 24 h. Only trace amounts of active drug appear in the urine [60]. Nifedipine dosage should be reduced in patients with hepatic impairment, and also in south Asians, who exhibit a slower metabolism of the drug, reflecting a longer terminal half-life of 8.6 h. As noted below, some data exist regarding the use of immediate-release nifedipine capsules for acute hypertension in children; however, no pharmacokinetic studies of this agent have been conducted in children to date.

Verapamil

Verapamil is a phenylalkylamine derivative that exhibits vasodilatory and antiarrhythmic effects, similar to diltiazem. Verapamil, like diltiazem, is indicated for the treatment of angina, hypertension, and arrhythmias. The drug is available in immediate-release, extended-release, controlled-onset extended release (COER-24) and injectable formulations. The immediate-release oral formulation has an initial onset of effect within 18 min and reaches peak plasma concentration in 1–2 h following administration. The extended-release formulation reaches a peak response approximately in the same time period as the immediate-release formulation, although peak concentrations are reached in 7–9 h [64].

Although absorption of an oral dose of verapamil exceeds 90%, its bioavailability is low, approximately 20–35%, because of extensive prehepatic first-pass metabolism. This is true for all formulations of verapamil, regardless of whether capsules are swallowed intact or sprinkled onto food [64, 65]. Approximately 83–93% of verapamil is bound by plasma proteins. Elimination half-life of verapamil is 2–7 h, although chronic use (>12 weeks) will prolong the half-life to 6.4–12 h [66]. Of the 12 metabolites of verapamil that have been identified, only norverapamil reaches appreciable concentrations in plasma. However, the cardiovascular activity of norverapamil is only a fraction of that of verapamil itself [64]. Approximately 70% of an oral dose of verapamil is excreted as metabolites in the urine. It is recommended that verapamil be used with caution in patients with impaired renal function, as prolongation of the PR interval may occur. At least one study of verapamil pharmacokinetics in children with hypertrophic cardiomyopathy or arrhythmias demonstrated decreased clearance in infants compared to older children [67]. However, no kinetic data exist for children treated with verapamil for isolated hypertension.

Special pharmacologic considerations

Renal effects

The most common therapeutic use of CCBs in children is for the treatment of hypertension. Since the majority of pediatric hypertension is of renal origin [2], it is important to consider the renal effects of these drugs. Such effects can be divided into immediate effects on renal physiology, and long-term renoprotective effects. In the short term, CCBs decrease mesangial cell proliferation, thereby decreasing receptor sites for angiotensin II. The clearance of macromolecules and superoxide free radicals is increased [68]. In the glomerulus, CCBs affect primarily the afferent arteriole, with little effect on the efferent arteriole or glomerular capillary pressure. The dilatation of the afferent arteriole helps reduce systemic blood pressure. Studies have demonstrated that during treatment of patients with essential hypertension, glomerular filtration rate and renal plasma flow increase and renal vascular resistance decreases [68], leading to changes in natriuresis and diuresis. For example, as mentioned above, short-term administration of felodipine has been demonstrated to both increase and decrease natriuresis and diuresis, depending on the dose administered [44]. However, most reports have indicated that patients maintained on CCBs for chronic therapy exhibited increases in sodium and water excretion that may contribute to their antihypertensive effects [69, 70].

With respect to long-term renal protection, a long-standing area of interest has been what effect, if any, CCBs have on proteinuria and the progression of proteinuric renal diseases. The original studies were conducted in proteinuric diabetic adults and demonstrated a

reduction in proteinuria with diltiazem, but not with nifedipine [71]. Diltiazem's effect was not as great as that produced by ACE inhibitors, and seemed to be dependent on blood pressure reduction as the mechanism, as opposed to a specific effect on intraglomerular hemodynamics [72]. Subsequent studies have confirmed that only the non-dihydropyridine CCBs reduce proteinuria, at least in adult patients with diabetic nephropathy [73, 74]. Animal studies conducted in the remnant kidney model have suggested that this difference may be related to a greater deleterious effect of dihydropyridine CCBs on renal autoregulation compared to non-dihydropyridine CCBs [75]. In contrast to patients with diabetes, patients with non-diabetic proteinuric renal diseases do not seem to benefit from treatment with non-dihydropyridine CCBs, and should be treated with ACE inhibitors [73, 74]. However, at least one recent study has demonstrated a beneficial effect of verapamil in proteinuric children [76], suggesting that perhaps other forms of renal disease may also be benefited from treatment with non-dihydropyridine CCBs. Clearly, further studies in large numbers of patients are needed to determine whether CCBs will play a significant role in the treatment of proteinuria in children.

Another important area of study has been the renal protective effect of CCBs in renal transplant patients also receiving cyclosporine and/or tacrolimus [77–80]. Although the exact mechanisms for the renal protective effect remain unknown, the effects of CCBs on renal hemodynamics discussed above probably play a significant role, especially the afferent arteriolar dilatation. Transplant recipients treated with CCBs have been shown to maintain normal sodium excretion in spite of cyclosporine-induced vasoconstriction [77]. Both short- and long-term graft function has been demonstrated to be superior in CCB-treated transplant recipients compared to patients not treated with CCBs [78, 79]. Such benefits appear to be independent of CCB antihypertensive effects [80]. Given these benefits, CCBs have found widespread use in the management of hypertension in pediatric organ transplant recipients [62].

Metabolism and drug interactions

As previously mentioned, most CCBs, with the exception of amlodipine, exhibit relatively low bioavailability despite the fact that they are avidly absorbed in the gastrointestinal tract. This is due to extensive prehepatic first-pass metabolism. Once reaching the liver, CCBs as a class are metabolized via the hepatic P450 enzyme system, specifically through the cytochrome P450 3A subfamily. It is this extensive hepatic metabolism that obviates the need for dose adjustment of most CCBs in patients with renal insufficiency (see above). However, several other important drugs are also metabolized via the P450 system, which sets the stage for potential drug interactions. An important example of this phenomenon was seen with mifebradil, which was ultimately pulled from the market because of numerous drug interactions [81].

When discussing drug interactions, it is important to understand if the drug causing the interaction is a hepatic enzyme inducer or inhibitor. Enzyme induction usually increases the amount of enzyme in the liver, resulting in an increase in the rate of drug metabolism, ultimately decreasing the area under the curve and potentially decreasing drug efficacy. Examples of enzyme inducers are drugs like phenobarbital, carbamazepine, rifampin, omeprazole, and phenytoin. On the other hand, other drugs can be enzyme inhibitors. Most drugs inhibit metabolism by inhibiting the hepatic mixed-function oxidase system. The most frequently reported clinical manifestation of inhibition of metabolism is toxicity of the inhibited drug, due to increased plasma concentrations of the inhibited drug. The problems resulting from enzyme inhibition usually can be avoided if inhibition is anticipated. Examples of enzyme inhibitors are allopurinol, erythromycin, isoniazid, ketoconazole, oral contraceptives, and valproic acid.

There are numerous drug interactions affecting the P450 enzyme system, but we are only going to discuss the most significant interactions pertinent to reported uses of CCBs in pediatric patients. The first one that deserves mention is cyclosporine A. In the study by Pfammatter et al. of 12 children treated with amlodipine, cyclosporine trough levels remained constant and no adjustments were needed [35]. However, in at least one adult study, amlodipine was reported to increase cyclosporine levels by 25–40% [82]. Other studies have not confirmed this finding [83]. Diltiazem is also known to increase levels of both cyclosporine and tacrolimus [84–87], an effect that has been utilized by some investigators to reduce the amount of cyclosporine administered [84]. Verapamil and nifedipine have also been reported to impair cyclosporine elimination in children [88]. While this is a well-documented effect of verapamil also seen in adults [89], nifedipine has usually been reported not to affect cyclosporine metabolism [89, 90]. Given these conflicting reports, it would clearly be prudent to closely monitor cyclosporine levels after starting a transplant patient on any CCB.

Another interaction of note is the interaction between the CCBs and antifungals of the azole class, fluconazole, itraconazole, and ketoconazole. The azoles inhibit the hepatic isoenzyme CYP3A4, which is involved in the metabolism of several CCBs, namely nifedipine, isradipine, nicardipine, amlodipine, and felodipine. This can cause increased serum concentrations of the CCB, and increase the risk of potential adverse effects, notably peripheral edema [91]. Felodipine also has reported drug interactions with carbamazepine, erythromycin, phenobarbital and phenytoin. Erythromycin can significantly increase the plasma concentration of felodipine, while the other drugs mentioned have caused a diminished efficacy of felodipine [45]. Conversely, diltiazem and verapamil can increase carbamazepine levels, leading to potential neurotoxicity [87]. Given these numerous interac-

tions, we would advise that practitioners caring for children with complex medication regimens either consult one of the available comprehensive reviews on the subject, or avoid those CCBs with the largest number of reported interactions, especially verapamil, diltiazem and felodipine.

Finally, it is also important to mention some issues related to the effect of food on CCB metabolism. As noted in the preceding discussions of individual CCBs, usually administering CCBs with food has little or no effect on their absorption, although there are a few exceptions (see above). The most notable drug-food interaction involving CCBs is the interaction with grapefruit juice, which has been demonstrated to increase the bioavailability and serum concentration of felodipine, amlodipine and other dihydropyridine CCBs [92, 93], primarily by suppressing the cytochrome P450 enzyme CYP3A4 found in the intestinal wall. This leads to a reduction in the usual first-pass metabolism of these agents discussed above. It is unclear at this time whether a similar effect would be seen in children, as all studies of this interaction have been conducted in adult subjects. In addition, whether this interaction would have a significant effect on blood pressure is also unknown. Given these uncertainties, it seems reasonable to caution patients that a potentially important interaction may exist, and that CCBs should probably be administered with liquids other than grapefruit juice.

Adverse effects

In general, CCBs as a class are well-tolerated medications, with a relatively low incidence of significant adverse effects [94]. Many adverse effects, including flushing and headache, are more common with the immediate-release preparations of these agents and appear to be dose related. Tachycardia is another frequently reported adverse effect of CCBs that is intrinsically related to the vasodilatation produced by these agents. Gingival hyperplasia and lower extremity edema are two unique adverse effects of CCBs that warrant further discussion. Gingival hyperplasia has been reported with several CCBs, including amlodipine, felodipine, nifedipine, and verapamil [94–96]. The mechanism of this phenomenon is unknown. Incidence rates vary between the CCBs listed, and appear to be lowest with amlodipine and greatest with nifedipine. Regression has been reported following a change in therapy from nifedipine to isradipine [97]. Lower extremity edema has also been reported with many CCBs, with an increased incidence at higher doses. The mechanism is thought to be related to a direct effect of the drugs on the local vasculature, as opposed to fluid overload [94, 98]. All the adverse effects mentioned here have been reported in children treated with CCBs. Specific comments regarding these effects in children will be discussed below.

Therapeutic use of CCBs in childhood hypertension

Although there have been few prospective studies of the safety and efficacy of CCBs in children, this class of antihypertensives has come into widespread use for treatment of hypertension in children and adolescents, and has been advocated for use as first-line antihypertensive therapy in children by several authors [1, 2]. In this section we will briefly review some of the published pediatric data that are available for these agents. Table 3 lists suggested doses for the drugs mentioned below; these doses are based upon published data as well as the authors' personal experience.

First-generation CCBs: verapamil, diltiazem and nifedipine

Although the first-generation CCBs have been in clinical use for over 15 years, little or no data exist regarding the efficacy of either verapamil or diltiazem in the treatment of pediatric hypertension. Most published data regarding verapamil use in children concern patients with either hypertrophic cardiomyopathy [99, 100] or arrhythmias [101]. Doses utilized for these indications have ranged from 3 to 5 mg/kg/day and appear to be well tolerated, although effects on blood pressure were not always reported. In our practice, we have occasionally utilized verapamil as an antihypertensive at the doses suggested in Table 2, generally with good efficacy. Concurrent treatment with beta-blockers, especially propranolol, should be avoided due to the possibility of prolonging the PR interval, which may result in heart block or even asystole [87, 102]. The availability of extended-release verapamil in numerous dosage strengths makes this a relatively convenient drug to use and titrate, although only in children old enough to swallow the relatively large tablets. The immediate-release verapamil tablets, however, can be crushed and made into a suspension.

For diltiazem, recently published uses in children have included treatment of pulmonary hypertension, muscular dystrophy and calcinosis [84, 103–106]. Reported doses used for those indications have ranged from 3 to 6 mg/kg/day and appear to be well tolerated. In the study of patients with muscular dystrophy, blood pressures were reported to be lower in the diltiazem-treated patients than in control patients by a factor of 12% for systolic pressure and 20% for diastolic pressure. Heart rate was slightly higher in the diltiazem group but this difference was not significant [105]. Another study of pediatric liver transplant recipients switched patients from nifedipine to diltiazem and demonstrated that treatment with diltiazem increased cyclosporine levels, allowing for a reduction in cyclosporine dose. The investigators demonstrated that renal function was stable in the diltiazem group compared to the nifedipine group, but did not specifically comment on diltiazem's effect on blood pressure [84]. Even with the limited blood pressure data reported in these studies, it can be deduced that

Table 3 Suggested doses for selected CCBs in children (*HTN* hypertension, *BP* blood pressure, *q.d.* once daily, *b.i.d.* twice daily, *t.i.d.* 3 times per day)

Drug	Starting dose	Dose interval	Maximum dose	Comments
Amlodipine	0.1–0.3 mg/kg/dose	q.d.–b.i.d.	0.6 mg/kg/day up to 20 mg/day	Long acting; dose adjustments should be 5-7 days apart; suspension may be compounded for infants and toddlers
Diltiazem	1.5–2 mg/kg/day	t.i.d.[b]	6 mg/kg/day up to 360 mg/day	Causes increased cyclosporine levels
Felodipine extended-release	0.1 mg/kg/day	q.d.–b.i.d.	0.6 mg/kg/day up to 20 mg/day	Tablet must be swallowed whole and is relatively large in size
Isradipine	0.05–0.15 mg/kg/dose	t.i.d.–q.i.d.[b]	0.8 mg/kg/day up to 20 mg/day	Rapidly acting; useful for both acute and chronic HTN; suspension may be compounded for infants and toddlers
Nicardipine intravenous	0.5–1.0 μg/kg/min	Continuous infusion	4–5 μg/kg/min	Continuous BP monitoring necessary; may cause reflex tachycardia
Nifedipine extended-release[a]	0.25–0.5 mg/kg/day	q.d.–b.i.d.	3 mg/kg/day up to 180 mg/day	Tablet must be swallowed whole and is too large for young children
Verapamil	3–4 mg/kg/day	t.i.d.[b]	8 mg/kg/day up to 480 mg/day	Concomitant administration of beta-adrenergic blockers should be avoided

[a] Sublingual administration of immediate-release preparation no longer recommended
[b] Immediate-release formulation. Extended release formulations also available that allow q.d.–b.i.d. dosing

diltiazem is probably an effective antihypertensive agent in children. As with verapamil, this conclusion is supported by our own experience using diltiazem in a small number of hypertensive children. However, it should be emphasized that because of the effects of verapamil and diltiazem on cardiac conduction, as well as the availability of newer compounds, these CCBs are not routinely used in the treatment of childhood hypertension.

In contrast to verapamil and diltiazem, there is quite a bit of published data regarding use of nifedipine for the treatment of childhood hypertension, although one caveat is that this literature is confined almost exclusively to the use of nifedipine for treatment of hypertensive emergencies. An important point to make here is that although the discussion that follows refers to "sublingual" administration of nifedipine, in reality, no absorption of the drug occurs in the mouth itself [107]; rather, it is likely that all absorption of the drug occurs in the gastrointestinal tract, with "sublingual" administration leading to more rapid onset of drug effect due to swallowing of the drug liquid. The same effect can be produced by biting then swallowing the capsule. However, since the term "sublingual" is so widespread in the literature, we will use it throughout this review to refer to this method of administration, keeping in mind that the drug actually does not begin to lower blood pressure until after it has been swallowed.

The first report of nifedipine use in treatment of acute hypertension was published in 1983 by Dilmen and colleagues [108], who administered 0.25–0.5 mg/kg/dose of nifedipine sublingually to 21 children with severe hypertension and found that it reduced blood pressure by approximately one-third within 30 min. Duration of effect was approximately 6 h, and reported side effects included tachycardia and flushing. Several similar reports appeared in the literature over the next several years [109–111], all concluding that in children experiencing hypertensive emergencies, sublingual nifedipine at doses ranging between 0.18 and 0.5 mg/kg/dose was an effective alternative to other agents that require parenteral administration such as hydralazine or sodium nitroprusside [108, 109]. Of note, some investigators reported that nifedipine had a shorter duration of effect than expected [109, 110], and at least one group cautioned against the use of nifedipine for symptomatic hypertensive emergencies in favor of drugs such as labetalol which can be titrated to response [111]. Despite these uncertainties, most recent recommendations for treatment of severe hypertension in children include sublingual nifedipine as a first-line agent [1–3, 112]. The advisability of continuing this practice in light of recent literature will be discussed below.

Use of nifedipine for treatment of chronic hypertension in children has received less attention. In fact, we could find no published reports of the efficacy of chronic nifedipine treatment, except for three studies in which hypertensive children receiving nifedipine chronically were switched to other CCBs [61, 62, 84]. Only one of these studies reported the mg/kg dose of nifedipine that the patients were receiving before being switched to the

alternative CCB [62]; these children were receiving 0.9±0.5 mg/kg of nifedipine per day, although it was not specified whether they were receiving immediate-release or extended-release nifedipine. In all three reports, patients' blood pressures were felt to be well controlled before they were switched to the alternative agent. Despite the lack of data, our experience and that of others is that nifedipine in its extended-release preparation is clearly an effective agent for chronic therapy of childhood hypertension, although the large tablet size (which cannot be crushed) limits its use to children mature enough to be able to swallow it. Twice-daily administration may be necessary to achieve good blood pressure control throughout an entire 24 h-period in children [61].

Second and third generation dihydropyridine CCBs

In contrast to the first generation CCBs, a reasonably large body of data has been published regarding the efficacy of second- and third-generation CCBs in children. Agents for which there is published efficacy data and that have found some use in children include isradipine, felodipine and amlodipine. Other drugs in this group that will not be discussed here include nitrendipine, nisoldipine and oral nicardipine.

One of the shortest-acting agents in this group is isradipine (Table 2). Data on its efficacy in pediatric hypertension has been published by two groups of investigators [52, 53]. Both reports demonstrated that isradipine treatment produced significant decreases in both systolic and diastolic blood pressure, ranging between 6–12% and 7–17%, respectively. Doses ranged from 0.1 to 0.8 mg/kg/day and side effects included tachycardia and flushing. Both reports noted that isradipine had a short duration of action, necessitating administration every 6–8 h. This is significantly different from the typical b.i.d. regimen used in adults [51]. An extemporaneous suspension may be compounded which has been shown to be stable for up to 30 days [113], permitting accurate dosing, even in infants and toddlers. An extended-release preparation is commercially available, although it has the disadvantage of a large tablet size. In our practice, isradipine has been found to be quite useful in the management of hospitalized children with acute hypertension. Blood pressure elevation in this setting may be relatively unstable, necessitating more frequent dose adjustments than usually recommended for longer-acting agents such as amlodipine. We have also found isradipine suspension to be extremely useful in treating infants with hypertension.

As noted above, felodipine is commercially available only as an extended-release preparation. Its effects on control of hypertension in children were investigated by Moncica and colleagues, who conducted a crossover trial of extended-release felodipine vs long-acting nifedipine in 21 children with renal hypertension [61]. They demonstrated improved BP control with once-daily felodipine compared to nifedipine, as demonstrated by a lower daytime BP load on ambulatory BP monitoring. However, nocturnal BP control was somewhat better during nifedipine treatment, which the authors speculated was due to its twice-daily dosing schedule. Doses of felodipine were not reported on a mg-per-kg basis, but were approximately 23% of the doses of nifedipine required by the same patients to achieve BP control (a second report by the same investigators on a subgroup of the patients in this study reported effective doses of 0.18–0.56 mg/kg/day [47]). The authors concluded that felodipine provided improved blood pressure control compared to nifedipine and also led to improved compliance because of the once-daily administration. Despite this, felodipine has not found widespread use in children, most likely because the extended-release tablet must be swallowed whole, making it impossible to use this drug in infants and young children.

The CCB that appears to have found the most widespread use is children is amlodipine, a lipophilic third-generation dihydropyridine drug with a longer duration of action than any of the CCBs discussed thus far [27–29]. This property is illustrated by studies in adults that have demonstrated effective blood pressure control with amlodipine even when a "missed dose" is incorporated into the study design [114]. As discussed previously, amlodipine's duration of action is related to the properties of the drug itself, rather than to the formulation of the tablet (as in the extended-release formulations of shorter-acting CCBs). Thus it should in theory retain its long duration of effect if the tablet were crushed or placed in suspension, making it an attractive agent for the treatment of hypertensive children. This has led to several reports of amlodipine in the treatment of pediatric hypertension, usually in children with secondary forms of hypertension [32–36]. Doses reported to be effective have varied widely, ranging from 0.09 to 0.8 mg/kg/day (Table 3), with several investigators reporting that children seem to require higher doses of amlodipine on a per kilogram basis than those recommended for adults, with the youngest children requiring the highest doses [32, 33, 36]. Another common finding in the pediatric studies of amlodipine efficacy is that children seem to require twice-daily administration of amlodipine to maintain effective BP control [32, 33], as opposed to the once-daily administration schedule that is utilized in adults. Whether twice-daily administration is truly necessary because of altered amlodipine pharmacokinetics in children, or whether it reflects the investigators' prescribing habits, is a question that should hopefully be answered by the multicenter pediatric amlodipine population pharmacokinetic study that is currently being conducted in the United States.

We have treated over 70 children with amlodipine, mostly patients with secondary hypertension, and have generally found that doses of 0.1–0.6 mg/kg/day are effective and well tolerated [33]. Adverse effects have included flushing, headache, lower extremity edema and fatigue, and generally respond to dose reduction. Infants and small children may be treated with amlodipine utiliz-

ing either crushed tablets [35], or by preparing an extemporaneous suspension [34, 115]. Amlodipine seems particularly well suited for treatment of hypertensive pediatric renal transplant recipients, a group of patients in whom CCBs are felt to have renal protective effects (see above). In short, although some problems await more detailed study, it appears as though amlodipine has deservedly found a place in the treatment of pediatric hypertension.

Intravenously administered CCBs

Of the commercially available CCBs, three may be administered intravenously: verapamil, diltiazem and nicardipine. A class IV antiarrhythmic agent, intravenous verapamil, slows conduction through the AV node, making it suitable for treatment of atrial arrhythmias, particularly supraventricular tachycardia [116]. Although there is one published study demonstrating the efficacy of intravenous verapamil for hypertension in adults [117], there are no similar data available for children. Therefore, although it is natural to assume that intravenous verapamil would lower BP in hypertensive children, its effects on cardiac conduction would suggest that it be reserved for use as an antiarrhythmic in this age group. Intravenous diltiazem has similar antiarrhythmic properties to verapamil [42], but we could find no data regarding its use as an antiarrhythmic in children, let alone its use as an antihypertensive. Given the widespread availability of other intravenously administered antihypertensives with demonstrated efficacy in children, we cannot endorse the use of intravenous diltiazem for this purpose.

Intravenous nicardipine has found widespread use in recent years for the treatment of hypertensive emergencies, particularly in the intensive care unit [ICU] setting. The ideal drug for this type of hypertension would lower blood pressure in a controlled manner, avoiding the risks associated with sudden falls in blood pressure (see below), and having little or no adverse effect on either the underlying disease or other aspects of the patient's clinical status [118, 119]. Traditionally, sodium nitroprusside has been the most widely used agent for hypertensive emergencies in children, with intravenous labetalol finding widespread use more recently [119]. When administered by continuous infusion, these agents produce a gradual, dose-related reduction in blood pressure that is easily reversible by slowing down or discontinuing the infusion. However, both have potentially significant side effects, including thiocyanate buildup with prolonged use of nitroprusside and induction of bronchospasm by labetalol in patients with reactive airways disease.

Nicardipine has been shown to be an effective antihypertensive agent in numerous studies in adults, comparing favorably to nitroprusside [120, 121]. Several reports have now appeared regarding the use of intravenous nicardipine in children with severe hypertension [122–125]. Treluyer and colleagues reported that intravenous nicardipine, administered as a continuous infusion at a dose of 1.0 μg/kg/min, produced a reduction in systolic blood pressure of 10–13% and a reduction in diastolic blood pressure of 17–26% within 1 h [122], without clinically apparent side effects. Other investigators have reported similar efficacy for intravenous nicardipine in hypertensive preterm infants [123]. The effective dose range reported by these investigators is summarized in Table 3. In our pediatric ICU, intravenous nicardipine has been effective in children with severe hypertension of many causes, ranging from solid organ transplant recipients to patients with respiratory failure receiving extracorporeal membrane oxygenation [125]. In contrast to Treluyer's report, we have found that reflex tachycardia may indeed occur with nicardipine administration, which is similar to data from studies in adults [54, 121]. As in adults, this effect is usually of no clinical significance. It should be mentioned that, as with any such patient, severely hypertensive children treated with intravenous nicardipine should be cared for in the intensive care setting so that blood pressure and the effects of treatment can be frequently monitored.

Safety concerns

Numerous concerns about the safety of CCBs have been raised in recent years, including possible effects of CCBs on reinfarction and mortality following acute myocardial infarction, increased risk of bleeding, cancer and depression in patients treated with CCBs, and adverse effects related to administration of short-acting CCBs, particularly sublingual nifedipine, for treatment of acute hypertension [126–130]. Although a detailed discussion of these issues is beyond the scope of this review, many of the initial reports have been contradicted by later, more carefully conducted studies and meta-analyses [131–134], several of which have demonstrated that the adverse cardiovascular effects of such drugs were not seen if longer-acting CCBs were used [133, 134]. In addition, it is difficult, if not impossible, to extrapolate the results of studies conducted in middle-aged and elderly adults with extensive cardiovascular disease to the treatment of children with isolated primary hypertension or hypertension secondary to renal disease. Although it would be folly to completely dismiss such safety concerns, none of these data would seem to argue for avoidance of CCBs in children.

However, one safety concern that does seem to warrant further discussion with respect to the treatment of pediatric hypertension would be the use of sublingual nifedipine for treatment of acute hypertension. Reports of cerebrovascular accidents following sublingual nifedipine use in adults with acute, severe hypertension [129, 135, 136] were followed by calls for a moratorium on the use of this drug for this indication [130, 137]. Although an informal survey of pediatric nephrologists conducted several years ago did not support such a moratorium in children [138], review of the literature reveals several case reports of sudden, profound hypotension in

hypertensive children treated with sublingual nifedipine [138–141]. Several of these children developed transient neurologic deficits similar to those reported in adults [138, 141]. We have seen several problems related to this effect of sublingual nifedipine in our own institution, including one case of severe hypotension in a liver transplant recipient that could potentially have led to hepatic artery thrombosis [142]. Furthermore, although methods have been published for withdrawal of the liquid within immediate-release nifedipine capsules for administration to infants and small children [143], we have found that the high concentration of nifedipine within the capsules [30 mg/ml for the Procardia brand (Pratt Pharmaceuticals Division, Pfizer Inc., New York, NY) 10 mg capsule] makes dispensing of exact doses cumbersome at best. In addition, there are differences in this concentration according to manufacturer, which could lead to dose errors if this difference were not recognized. For these reasons, we have replaced sublingual nifedipine with other agents in our own institution, typically either intravenous labetalol [144] or oral minoxidil [145], and would urge other practitioners to do likewise.

Finally, no discussion of CCB safety in children would be complete without a brief mention of problems related to long-term use on growth and development. Given the diverse effects of calcium within the body, and especially the effects within the cardiovascular system, there are certainly potential grounds for concern. For example, the efficacy of CCBs in the treatment of children with hypertrophic cardiomyopathy [100] suggests that CCBs may inhibit myocardial growth in a manner similar to their effects on vascular smooth muscle cell growth [146]. Chronic activation of the sympathetic nervous system by dihydropyridine CCBs [147] raises the possibility that long-term use of CCBs may eventually have similar adverse effects on cardiovascular morbidity and mortality in pediatric patients as in adults, perhaps manifesting in young adulthood after 1 or 2 decades of CCB treatment. Unfortunately, all of the published data currently available for pediatric use of CCBs concerns short-term efficacy and safety – usually from studies of only several weeks duration. Furthermore, all of the ongoing industry-sponsored trials of CCBs in children are also of extremely short duration, typically 12 weeks or less. Although the written requests from the Food and Drug Administration under the auspices of the FDA Modernization Act of 1997 [148] for pediatric studies of CCBs have included requests for data on long-term effects in children (Anne Cropp, PharmD, personal communication), it is likely that such data will not be collected unless pediatric investigators design and conduct appropriate trials (which would clearly need to be of many years duration and therefore extraordinarily difficult to complete). Therefore, while it is reasonable to raise the question regarding long-term effects of CCBs in children, at present there are no data available with which to address these concerns.

Conclusions

Calcium channel blockers are a diverse group of antihypertensive agents with significant pharmacokinetic differences. Although the available data regarding use of these agents in children is limited, CCBs appear to be both effective and well tolerated in hypertensive children, and can be utilized for the treatment of hypertension in many different clinical settings. Given the recent developments in the United States with respect to pediatric drug trials spurred by the Food and Drug Modernization Act of 1997 [148], we are hopeful that well-designed trials of CCBs in children will be conducted in order to answer the remaining questions regarding pediatric use of CCBs.

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