

REVIEW

Mitigation of calcium channel blocker-related oedema in hypertension by antagonists of the renin–angiotensin system

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This review is aimed at examining calcium channel blocker (CCB)-related oedema and how this can be attenuated through the use of agents that inhibit the renin–angiotensin system. CCBs are effective antihypertensive agents, but their propensity for causing oedema may reduce compliance. A review of the literature has indicated that the absolute incidence of this side effect is difficult to determine because reported rates vary widely, a factor that may stem from differences in the surveillance technique (active vs passive). In a recent trial incorporating active surveillance, 25% of patients who received amlodipine 10 mg per day experienced oedema. CCB-induced oedema is caused by increased capillary hydrostatic pressure that

results from preferential dilation of pre-capillary vessels. Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) cause post-capillary dilation and normalize hydrostatic pressure, and are thus ideally suited for prevention/reversal of CCB-induced oedema. The efficacy of this strategy was proven using both subjective and objective techniques. ARB/CCB and ACEI/CCB combination therapy is also more effective than CCB monotherapy in controlling blood pressure. These combinations represent an important advance in the management of hypertension.

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Introduction

The majority of hypertensive patients require combination therapy with two or more antihypertensive agents from different classes to achieve their target blood pressure (BP).^{1,2} Compared with monotherapy, low-dose combination therapy has the dual advantages of providing more effective BP control and minimizing the risk of side effects.^{1,2} The combination of a calcium channel blocker (CCB) and an angiotensin receptor blocker (ARB) represents a new and potent option in the management of hypertension. This combination, which is recommended for use by the current guidelines,^{2,3} is highly effective in reducing BP in hypertensive patients.^{4–8}

When used as monotherapy, CCBs are associated with a substantial risk of peripheral oedema,^{9–12} a side effect that may reduce patient compliance or necessitate switching to a different drug.^{13,14} The incidence of oedema in CCB-treated patients can be

substantially reduced by addition of an inhibitor of the renin–angiotensin system (RAS), that is, an ARB or an angiotensin-converting enzyme inhibitor (ACEI).^{5,6,15–22} This review discusses the pharmacological mechanisms that underlie CCB-induced oedema formation and mitigation of this side effect by ACEIs and ARBs. The data cited in this review were selected for relevance by the author from searches performed using PubMed without specific considerations to patient populations. Data showing the incidence of CCB-related oedema in clinical trials are summarized and the potential effects of data-collection techniques on the reported incidence of this adverse event are discussed.

Mechanism of CCB-induced oedema

Dihydropyridine CCBs are second only to the arteriolar dilators (for example, minoxidil, hydralazine) as a cause of vasodilatory oedema in patients receiving antihypertensive therapy^{9,10,21}. CCB-induced oedema is caused primarily by the increased capillary hydrostatic pressure that results from greater dilation of pre-capillary than post-capillary vessels.^{9,10,12,23} This effect may be mediated, in part, by the greater sensitivity of resistance vessels than capacitance vessels to CCB-induced reductions

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in myogenic vascular reactivity,²⁴ and may be augmented by CCB-induced reductions in postural vasoconstriction.²⁵

Because the oedema is related to the mechanism of action of dihydropyridine CCBs, it represents a class effect. Claims that third-generation, long-acting CCBs are associated with lower rates of oedema than older drugs have been investigated in a number of clinical trials. However, when reported by patients as 'leg swelling', one of these third-generation CCBs has been associated with an oedema incidence of 22%.²⁶ Thus, although differences among CCBs in oedema incidence rates have been reported in a number of studies,^{10,27–30} it is evident that dose-dependent peripheral oedema remains a common side effect in patients receiving both established and newer CCBs.^{10,31}

Factors that may influence oedema

Several factors can predispose the patient to an increased risk of oedema.

The increased incidence of oedema in women compared with men has been related earlier to comparatively higher rates of self-observation and lower tolerance to cosmetic change.¹⁰

Obesity is a predisposing factor of oedema and may be associated with elevated ventricular filling pressures and cardiac output^{32,33} and chronic venous insufficiency.³⁴ Obesity is also correlated with conditions such as obstructive sleep apnoea,³⁵ which also cause oedema.³⁶

Advancing age increases the likelihood of CCB-induced oedema; as the interstitial tissue ages, it is less able to counterbalance hydrostatically driven oedema and thus the elderly are more likely to have greater levels of CCB-induced oedema.³⁷ Furthermore, an upright posture also increases the hydrostatic pressure of the legs and can result in an increased incidence of CCB-induced oedema.³⁸

Mitigation of CCB-induced oedema

As CCB-induced oedema is primarily related to vasodilation and not to fluid retention,^{10–12,23,39} coadministration of a diuretic is not a logical strategy for alleviation of this side effect.¹⁰ In contrast, agents that cause post-capillary dilation (for example, ACEIs and ARBs) are ideally suited for the prevention or reversal of CCB-induced oedema because the normalization of intracapillary pressure induced by these agents will reduce fluid extravasation (Figure 1).^{10,12,22} This theoretical concept is borne out by the results of individual clinical trials that have shown that the incidence of oedema is substantially lower in patients who receive ACEI/CCB or ARB/CCB combination therapy than in those treated with CCB monotherapy.^{6,15–22} Moreover, a meta-analysis of 82 studies that compared the safety and efficacy of benazepril/amlodipine therapy with

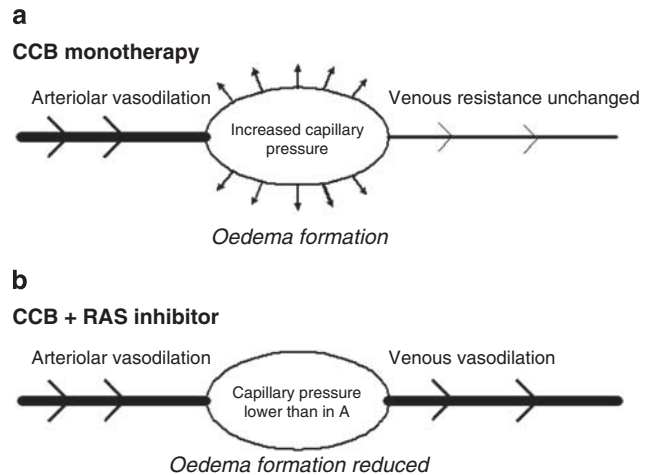


Figure 1 Effects of calcium channel blockers (CCBs), administered with and without a renin-angiotensin system (RAS) inhibitor, on capillary pressure and oedema formation (Figure redrawn from Figure 2 of Epstein *et al. Drugs* 2007;67:1309–1327). (a) CCB monotherapy; (b) CCB + RAS inhibitor. Dihydropyridine CCBs cause selective vasodilation of the arteriolar side of the circulation. Administration of CCBs as monotherapy causes increased pressure within the capillary bed, leading to fluid transudation and oedema formation. Inhibitors of the RAS, that is, angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) cause both arteriolar and venous vasodilation. Addition of an ACEI or an ARB to a regimen of CCB monotherapy reduces the pressure within the capillary bed, thereby ameliorating the oedema.

that of nine monotherapy regimens concluded that this combination was associated with a lower overall rate of side effects and of side effects that led to withdrawal than either amlodipine or nifedipine monotherapy.⁴⁰

Table 1 shows the rates of oedema from eight relevant clinical trials. Although the incidence of oedema recorded in the CCB monotherapy groups varies widely (range, 4.9–34.4%), the data are consistent in showing lower rates of this side effect in the patients who receive ACEI/CCB or ARB/CCB combination therapy. These reductions can be substantial. For example, in one recent trial, addition of olmesartan medoxomil 40 mg to amlodipine 10 mg reduced the placebo-subtracted rate of oedema by more than 50%.⁵ In an additional study, the incidence rate of peripheral oedema was lower with valsartan and amlodipine in combination (5.4%) than with amlodipine monotherapy (8.7%).⁶ Moreover, in the trials summarized in Table 1 that recorded the highest incidences of oedema in CCB monotherapy-treated patients, addition of an ACEI or an ARB to the daily therapeutic regimen (benazepril 10 mg added to amlodipine 5 mg;¹⁶ valsartan 160 mg added to amlodipine 10 mg¹⁷) reduced the incidence of ankle oedema significantly.

The technique used in the assessment of oedema is obviously important in ensuring the validity of any study that aims to document the incidence of this side effect. Determinations regarding the presence or absence of peripheral oedema have

Table 1 Incidence of oedema in patients treated with CCB monotherapy, or with ACEI/CCB or ARB/CCB combination therapy

Trial design	Definition of oedema	CCB monotherapy			ACEI/CCB or ARB/CCB combination therapy			Reference
		Regimen and treatment duration	n	Incidence of oedema (%)	Regimen and treatment duration	n	Incidence of oedema (%)	
Placebo-controlled, double-blind, randomized, parallel group	All types, including dependent and leg Peripheral	Amlodipine 5 mg od; 8 weeks	77	16.9	Amlodipine 5 mg+benazepril 20 mg od; 8 weeks	77	7.8	Kuschnir <i>et al.</i> ²⁰
Placebo-controlled, double-blind, randomized, parallel group, factorial		Felodipine ER 2.5, 5, or 10 mg od; 8 weeks	176	10.8	Felodipine ER 2.5, 5, or 10 mg+enalapril 5 or 20 mg od; 8 weeks	319	4.1	Gradman <i>et al.</i> ¹⁸
Single/double-blind, randomized, forced titration	All types, including dependent, generalised, facial, and peripheral	Amlodipine 5 mg od; 4 weeks	144	4.9	Amlodipine 5 mg+benazepril 20 mg od; 8 weeks	137	1.5	Messerli <i>et al.</i> ²¹
Single/double-blind, randomized, forced titration	All types, including dependent, generalised, facial, and peripheral	Amlodipine 5 mg od; 4 weeks	144	4.9	Amlodipine 5 mg+benazepril 10 mg od; 8 weeks	138	2.2	Messerli <i>et al.</i> ²¹
Double-blind, randomized, crossover	Ankle	Amlodipine 5 mg od; 4 weeks	32	34.4	Amlodipine 5 mg+benazepril 10 mg od; 4 weeks	32	9.4	Fogari <i>et al.</i> ¹⁶
Placebo-controlled, double-blind, randomized, factorial	Combined ^a	Amlodipine 10 mg od; 8 weeks	163	24.5	Amlodipine 10 mg+olmesartan medoxomil 40 mg od; 8 weeks	162	11.2	Chrysant <i>et al.</i> ⁵
Open-label, randomized, crossover	Ankle	Amlodipine 10 mg od; 6 weeks	80	30.0	Amlodipine 10 mg+valsartan 160 mg od; 6 weeks	80	7.5	Fogari <i>et al.</i> ¹⁵
Randomized, crossover	Ankle	Manidipine 10 mg od; 6 weeks	40	7.5	Manidipine 10 mg+delapril 30 mg od; 6 weeks	40	2.5	Fogari <i>et al.</i> ¹⁷
Placebo-controlled, double-blind, randomized, parallel group	Peripheral	Amlodipine 2.5, 5 or 10 mg od; 8 weeks	460	8.7	Amlodipine 2.5, 5 or 10 mg+valsartan 40, 80, 160, or 320 mg od; 8 weeks	1437	5.4	Philipp <i>et al.</i> ⁶

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; ER, extended release; od, once daily.

^aIncluded any instance of oedema, peripheral oedema, pitting oedema, generalized and localized oedema, corrected for placebo.

Table 2 Effects of ACEIs and ARBs on CCB-induced peripheral oedema

End point	Baseline	CCB monotherapy (drug/daily dose)	ACEI or ARB monotherapy (drug/daily dose)	CCB+ACEI or CCB+ARB combination therapy (drug/daily dose)	Reference
<i>Lower limb volume</i>					
Mean \pm s.e.m. (ml)	1246 \pm 69	1568 \pm 84* (nifedipine 40 mg)	1297 \pm 69 (captopril 100 mg)	1297 \pm 85 (nifedipine 40 mg+captopril 100 mg)	Guazzi <i>et al.</i> ¹⁹
Mean \pm s.d. (ml)	1244 \pm 384	1419 \pm 301 (amlodipine 5 mg)	ND	1323 \pm 316 (amlodipine 5 mg+benazepril 20 mg)	Weir <i>et al.</i> ^{4,2}
Mean \pm s.d. (ml)	1296 \pm 144	1518 \pm 170* (amlodipine 5 mg)	1288 \pm 145 (benazepril 10 mg)	1379 \pm 152** (amlodipine 5 mg+benazepril 10 mg)	Fogari <i>et al.</i> ¹⁶
Mean \pm s.d. (ml)	1284 \pm 152	1582 \pm 177 (amlodipine 10 mg)	1296 \pm 141 (valsartan 160 mg)	1372 \pm 154** (amlodipine 10 mg+valsartan 160 mg)	Fogari <i>et al.</i> ¹⁵
Percentage change from baseline	ND	7.9* (manidipine 10 mg)	-0.8 (delapril 30 mg)	3.3** (manidipine 10 mg+delapril 30 mg)	Fogari <i>et al.</i> ¹⁷
<i>Pretibial subcutaneous tissue pressure</i>					
Mean \pm s.d. (cm H ₂ O)	2.09 \pm 1.74	3.67 \pm 2.16 (amlodipine 10 mg)	2.10 \pm 1.72 (valsartan 160 mg)	2.56 \pm 81** (amlodipine 10 mg+valsartan 160 mg)	Fogari <i>et al.</i> ¹⁵
Mean \pm s.d. (cm H ₂ O)	2.16 \pm 1.85	3.56 \pm 2.29* (amlodipine 5 mg)	2.12 \pm 1.91 (benazepril 10 mg)	2.71 \pm 1.84** (amlodipine 5 mg+benazepril 10 mg)	Fogari <i>et al.</i> ¹⁶
Percentage change from baseline	ND	36.6* (manidipine 10 mg)	-0.9 (delapril 30 mg)	10.4** (manidipine 10 mg+delapril 30 mg)	Fogari <i>et al.</i> ¹⁷

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; ND, no data; s.d., standard deviation; s.e.m., standard error of the mean. * $P < 0.01$ vs baseline; ** $P < 0.05$ vs CCB monotherapy.

typically been subjective but, recently, attempts have been made to assess limb oedema objectively by measuring limb volume and subcutaneous tissue pressure. Limb volume can be determined using the technique of water displacement, in which the lower limb is placed into a water-filled vessel and the weight or volume of water displaced is measured.^{15,17,41,42} Subcutaneous tissue pressure has been measured using the balancing open system, in which the subcutaneous environment is connected to a water manometer through a saline-filled needle and graduated capillary tube.^{15,16} Once the needle has been threaded into the subcutaneous space, tissue pressure causes movement of the meniscus in the capillary tube. A micropump connected to the manometer is used to achieve a pressure within the system at which there is no movement of the meniscus in the capillary tube. This pressure corresponds to the subcutaneous tissue pressure. Assessments of limb volume using the water displacement technique and of subcutaneous tissue pressure using the balancing open system are associated with good reproducibility (coefficients of variation: limb volume, 0.30%; subcutaneous tissue pressure, 0.25%^{15,17}).

Limb volume and subcutaneous tissue pressure measurements have been used to quantify the beneficial effects of ACEIs and ARBs on CCB-induced peripheral oedema.^{15-17,41,42} As expected, CCB monotherapy significantly increases both lower limb volume and pretibial subcutaneous tissue pressure,^{15,16,19} and these deleterious changes are ameliorated by addition of an ARB or an ACEI to the antihypertensive regimen (Table 2).¹⁵⁻¹⁷

Clinical trials may underestimate the incidence of CCB-induced oedema

In clinical practice, the incidence of a recorded outcome is heavily dependent on the reporting system used. Thus, substantially higher rates of disease and adverse events are consistently reported by active surveillance systems than by passive systems.⁴³⁻⁴⁸ This dependence of adverse event incidence on the method of data collection may also hold true for the rates of oedema reported in clinical trials involving CCBs, as it is evident that very different oedema incidence rates have been reported in CCB-treated groups in different clinical trials.^{6,17,49-51} Moreover, the data in Table 1 show that, even within one therapeutic regimen (amlodipine 5 mg per day), there is wide variation in the reported incidence of oedema (range, 4.9-34.4%). It should be noted that the definition of oedema varied among studies. The rigour with which signs of this adverse event were identified in these trials is not known, but the data suggest that differences in study design may have been a contributing factor. The literature contains a number of examples pertaining to CCB therapy that support this contention. For

example, Hermans *et al.*²⁸ reported the results of a double-blind, parallel-group study that incorporated two different patient-based methods of assessing the tolerability of isradipine and amlodipine (spontaneous reporting and completion of a questionnaire that included specific side effects known to be related to the use of dihydropyridine CCBs). After 6 weeks of therapy, amlodipine-treated patients assigned to the 'spontaneous reporting' system recorded an oedema incidence of 14.7%. In contrast, this side effect was reported by 19.4% of patients who completed the questionnaire.²⁸ In a second example, physical examination of CCB-treated patients by the investigator led to a reported oedema incidence of 10%.²⁶ However, when patient reports of 'leg swelling' were used as the assessment criterion for oedema in the same study, the incidence was 22%. There is also evidence that patients do not report all symptoms that they suspect to be related to drug administration to their doctor, and that physicians do not always record symptoms reported to them by patients.⁵² These findings show that the methods of data reporting and collection should be borne in mind while assessing the absolute incidence of adverse events reported by any clinical trial.

Although passive surveillance systems typically report lower rates of disease and adverse events than active systems, both can be used to assess the relative risks of a particular adverse event in two or more patient groups. Thus, the shortcomings of passive recording do not call into question the consistent evidence that addition of an ACEI or an ARB to CCB-based therapy leads to a reduction in the incidence of peripheral oedema.^{6,15–22}

Reduction of CCB-induced oedema may improve compliance

Compliance with therapy is a key factor in the effective management of hypertension, but both persistence and compliance are notoriously poor in hypertensive patients.^{53,54} Of the many reasons that may underlie this, increased complexity of the therapeutic regimen and adverse side effects are two of the best documented.^{55–60} Selection of a regimen that takes these factors into account is thus likely to increase compliance, improve antihypertensive efficacy, and reduce hypertension-associated morbidity and mortality.

Peripheral oedema—the major side effect of CCB therapy—is a source of distress for many patients⁶¹ and its onset may reduce compliance or lead to CCB-dose reduction or withdrawal.^{13,14} However, CCBs are highly effective agents that play an important role in the management of hypertension.^{1,2} Moreover, this class of drug is associated with a range of beneficial effects, including a reduction in the rate of progression of carotid atherosclerosis.² Attempts should therefore be made to retain these agents in

the therapeutic regimen by utilizing strategies that reduce the incidence of oedema, thereby increasing patient satisfaction and compliance. As discussed earlier, diuretics have no effect on the mechanism of CCB-induced oedema (selective arteriolar vasodilation),¹⁰ and use of this class of drugs in combination with a CCB is therefore not logical if amelioration or prevention of vasodilatory oedema is the aim. In contrast, the post-capillary vasodilation provided by ACEIs and ARBs is effective in ameliorating CCB-induced oedema.^{6,15–22}

If maximization of compliance is the aim, the side effect profile of the RAS inhibitor used should also be considered. As ARBs typically have a side effect profile similar to that of placebo and ACEIs have a propensity to cause cough,⁶² it may be preferable to choose an ARB for combination with a CCB. Certainly, the results of clinical trials show that ARB/CCB combination therapy is well tolerated.^{5,6,10,18,20,21}

Efforts to maximize compliance should also consider the treatment regimen itself. It is known that compliance is inversely related to both the number of medications and the number of daily doses prescribed.^{56,63} Compliance may therefore be improved by selecting a simple therapeutic regimen that minimizes both these factors.⁵⁶ For this reason, fixed-dose combinations may be preferred^{1,2} for CCB-treated patients receiving concomitant treatment with an ACEI or an ARB.

Other advantages of CCB/RAS inhibitor combination therapy

The significant beneficial effects of ARB and ACEI coadministration on CCB-induced oedema have been summarized above. However, combined use of a CCB and an agent that inhibits the RAS is beneficial for a number of other reasons. First, as CCBs and RAS inhibitors effect vasodilation by different mechanisms, their antihypertensive effects are additive when used in combination.^{5–8,64,65} This effect is exemplified by data from a recent trial involving amlodipine and olmesartan medoxomil, which showed that both the absolute BP reductions achieved and the rate of target BP attainment were significantly greater in patients who received combination therapy than in those who received amlodipine monotherapy.⁵ It is important to note that, in contrast to many other studies, the target BP in this trial was defined using both diastolic blood pressure and systolic blood pressure (<140/90 mm Hg for the majority of patients; <130/80 mm Hg for those with diabetes).⁵ The goals were thus in alignment with those recommended in the current guidelines for the treatment of hypertension.^{1,2}

A second reason for combining CCBs and RAS inhibitors is that the natriuretic effect of CCBs⁶⁶ augments the antihypertensive effect of ACEIs.^{67,68}

Furthermore, coadministration of an ACEI counteracts the RAS and sympathetic nervous system activation induced by CCBs.^{67,69} ARBs also reduce the activity of these systems in CCB-treated patients⁷⁰ and are therefore likely to have a similar beneficial effect.

These complementary pharmacological and side effect profiles of CCBs and ACEIs/ARBs are an excellent example of the principle—espoused in current hypertension guidelines^{1,2}—that use of combination therapy rather than monotherapy can lead to improvements in both efficacy and tolerability. Moreover, it is now acknowledged that the majority of hypertensive patients require combination therapy to achieve their BP goal.^{1,2}

The choice of individual agents to be used in an ACEI/CCB or ARB/CCB combination regimen will depend on a number of factors, including physician preference, availability, cost, tolerability and efficacy. As achievement of target BP is of primary importance in all hypertensive patients, efficacy should be a major criterion when selecting agents for use in any regimen.

It is anticipated that differences in efficacy among ARBs when used as monotherapy will be sustained when these agents are used in combination with hydrochlorothiazide.⁷¹ The same is likely to be true of ARBs when used in combination with CCBs, and of ACEIs and CCBs when used as part of dual-therapy regimens. The efficacy of antihypertensive agents when used as monotherapy should thus be taken into account when selecting agents for use in a combination regimen.

Conclusion

Calcium channel blockers are an effective class of antihypertensive agent, but their use is associated with increased risk of peripheral oedema. The true rate of CCB-induced oedema is difficult to determine, however, because incidence data reported in clinical trials vary widely. These variations are more likely to stem from differences in methods of adverse event recording (active vs passive) than from real differences in oedema rates. There is no doubt, however, that adding an agent that inhibits the RAS (that is, an ACEI or an ARB) to CCB monotherapy substantially reduces the incidence of oedema. This reduction in risk stems from the complementary pharmacological mechanisms of these agent classes.

In addition to reducing the incidence of oedema, adding an ACEI or an ARB to CCB monotherapy leads to improved efficacy. Fixed-dose ARB/CCB combination treatment represents an effective and well-tolerated option for the management of hypertension, and it is anticipated that the advent of a fixed-dose combination treatment that uses the most potent agents available in these classes will advance the management of hypertension still further.

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Conflict of interest

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