How should ankle oedema caused by calcium channel blockers be treated?

Prepared by UK Medicines Information (UKMi) pharmacists for NHS healthcare professionals
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Background

Peripheral oedema, most commonly of the ankles, is a well established adverse drug reaction of calcium channel blockers (CCBs)\(^1\)\(^2\) although the propensity to cause this may vary between different drugs within the class (See Medicines Q&A number 322.1 What are the reported incidences of ankle oedema with different calcium channel blockers? ).

The oedema caused by calcium channel blockers does not appear to be related to fluid retention, but due to an increase in capillary pressure leading to leakage of fluid\(^2\). For a more details on the mechanism of oedema formation, please refer to Medicines Q&A No 322.1. Dihydropyridine CCBs actually appear to have some inherent diuretic actions, yet can still cause oedema as an adverse reaction\(^3\).

Any patients who present with ankle oedema should first be assessed to rule out other causes\(^4\).

Answer

Treatment of ankle oedema will depend on the severity and other patient factors, with mild oedema not requiring specific treatment provided it is not troublesome to the patient\(^5\). Whilst ankle oedema associated with calcium channel blockers is rarely clinically serious, it may significantly reduce adherence to these potentially useful agents\(^6\).

Non-Pharmacological methods

Elevation of legs when in a prone position, or graduated compression stockings, may be an option in some patients with mild oedema\(^5\). However, there is little evidence to suggest these methods may be effective in reducing oedema.

Dose adjustments

As ankle oedema is dose related (although not necessarily in a dose-proportional manner), reducing the dosage of a CCB may lead to ankle oedema reducing in severity\(^6\).

CCB switching

Switching to another CCB class may reduce ankle oedema, although current evidence on the success rates of this strategy are conflicting. If a patient on a DHP agent reports oedema, a switch to a non-dihydropyridine such as verapamil, if clinically suitable, may lead to resolving of ankle oedema\(^5\). For relative reported incidences of ankle oedema, please see Medicines Q&A no 322.1.

Diuretics

Unlike other types of oedema, diuretics appear to have little effect on CCB-induced oedema\(^1\), even where there is large natriuresis and a subsequent decrease in plasma volume\(^3\). This applies to both thiazide and loop diuretics, and is due to the fact that diuretics act by reducing water retention only, and do not affect vasodilatory induced fluid pooling\(^2\). In fact, CCBs are thought to have natriuretic properties which are thought to contribute to their blood pressure lowering effects, but do not appear to preclude the formation of ankle oedema\(^3\).

In a small open label pilot trial, 25mg of hydrochlorothiazide was found to lead to a mean reduction in lower extremity oedema (as measured by a water displacement method) of 136.3ml. This was significantly less than the reduction found due to benazepril, an angiotensin converting enzyme inhibitor (ACEI) (see under ACEIs below)\(^7\).
Angiotensin Converting Enzyme Inhibitors (ACEIs)

It has been demonstrated in several trials that adding an ACEI to a CCB reduces the incidence of ankle oedema, although the mechanism by which this occurs is not currently known, but may be due to the dilation of venous capacitance vessels, which may then lead to a reduction in capillary hypertension and therefore leakage of fluid into the surrounding tissues. It is currently unknown whether any ACEIs are superior in treating ankle oedema, but any ACEI initiated should be dosed according to blood pressure lowering effect.

A randomised, double blind trial of amlodipine alone vs amlodipine in combination with ramipril found a lower prevalence of oedema in the combination therapy group (7.6%) compared to the monotherapy group (18.7%, P=0.011).

A small (n=47), open label trial found that patients who used benazepril concomitantly with amlodipine reduced water displacement by 204.4ml, which was significantly higher than the diuretic used as a comparator group. The usefulness of this trial is limited by its small size and the fact that the ACEI and diuretic used are not considered gold standard treatment in the UK at this time.

A recent review found that a combination of a calcium channel blocker along with an angiotensin system blocker combination led to 38% fewer incidences of peripheral oedema than with a calcium channel blocker alone. This review was limited to Medline and Cochrane databases only and did not differentiate between ACEIs and angiotensin II receptor blockers (ARBs)

Angiotensin II Receptor Blockers (ARBs)
The mechanisms by which ARBs reduce incidence of CCB induced ankle oedema remains unknown, but are likely to be similar to that involved when ACEIs are added to CCB therapy.

One open-label, blinded end point study found a significant reduction in the incidence of markers of ankle oedema (Ankle-foot volume and pretibial subcutaneous tissue pressure) in the group treated with valsartan in addition to amlodipine therapy vs. amlodipine alone, along with significantly reduced blood pressure, suggesting that in patients who are not able to tolerate ACEIs, and ARB may be an effective alternative for treatment of oedema.

A more recent study by the same authors compared valsartan and olmesartan effectiveness at reducing ankle oedema caused by amlodipine in a similarly designed study. Both ARBs reduced foot volume, but valsartan reduced oedema significantly more than olmesartan.

Nitrates
Nitrates, due to their venodilating action, may be offer some useful effects in treating CCB induced ankle oedema, but their use are limited by the practical considerations of having a stop-start regimen so tolerance does not develop.

Discontinuation
If other treatment options fail, discontinuing the CCB, and switching to an antihypertensive from another class of drugs, may be required.

Summary
Ankle oedema is a common, often troublesome adverse effect for patients who are receiving CCB therapy, and may affect compliance. It is usually refractory to diuretic treatment as it is due to changes in capillary pressure leading to leakage into interstitial areas, rather than due to water retention.

Treatment strategies include:

- Non-pharmacological interventions
- Dosage adjustments
- Switching to a non-DHP CCB
- Adding an ACEI or ARB
- Adding a nitrare
- Discontinuation of CCB
Of these options, the strongest evidence base is for adding in an ACEI. ARBs may be used in patients in whom ACEIs are not tolerated.

**Limitations**
This Medicines Q&A gives only a general guide to the different strategies available for treating CCB related oedema. Individual patient factors will impact on choice of treatment strategy.

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**Quality Assurance**

**Prepared by**
Hayley Johnson, Regional Drug and Therapeutics Centre

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**Checked by**
Sahima Rahman, Regional Drug and Therapeutics Centre

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**Search strategy**
Embase:
*Leg compression AND *calcium channel blocking agent AND *ankle edema
*Diuretics AND *calcium channel blocking agent AND *ankle edema
*ACEIs AND *calcium channel blocking agent AND *ankle edema
*ARBs AND calcium channel blocking agent AND *ankle edema
*Nitrates AND calcium channel blocking agent AND *ankle edema

Medline ("cut and paste" whole search strategy)
*Stockings, compression AND *calcium channel blockers AND *edema
*diuretics AND *calcium channel blockers AND *edema
*Angiotensin-Converting Enzyme Inhibitors AND *calcium channel blockers AND *edema
*Angiotensin 2 Receptor Blockers AND *calcium channel blockers AND *edema
*Nitrates AND *calcium channel blockers AND *edema

**References**
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7 Weir MR, Rosenberger C, and Fink JC. Pilot study to evaluate a water displacement technique to compare effects of diuretics and ACE inhibitors to alleviate lower extremity edema due to dihydropyridine calcium antagonists. American Journal of Hypertension 2001; 14(9): 963-968