What are the reported incidences of ankle oedema with different calcium channel blockers?

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

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Date prepared: 13th May 2013

Background

Calcium Channel Blocking agents (CCBs) are a diverse group of drugs which share a common mechanism of action, and have blood pressure lowering abilities\(^1\). Peripheral oedema, including ankle oedema, is a recognised adverse effect of the calcium channel blocking agents which may limit their usefulness, particularly in an aging population who are more likely to have co-morbidities\(^2,3,4\). Ankle oedema can range from being mild and unnoted to severely affecting quality of life\(^5,6\).

The risk of developing ankle oedema whilst using CCB therapy appears to be higher in women, older patients, those with heart failure, upright postures, and those in warm environments\(^6,7\).

Answer

Mechanism of ankle oedema:
The mechanisms by which CCBs give rise to ankle oedema are not currently understood. Proposed mechanisms include an increase in capillary pressure, resulting in fluid loss from the capillaries, or by interference with local vascular control\(^4\).

Unlike peripheral oedema caused by fluid retention, CCB-induced oedema appears to be due to redistribution of fluid from capillaries to interstitial spaces. Oedema caused by CCBs seems unaffected by diuretic treatment, suggesting it may be due to fluid pooling rather than fluid retention\(^5,6,8\). Oedema occurs despite CCBs possessing inherent diuretic effects\(^5,6\).

As well as the above possible mechanisms, CCB therapy blocks reflex increases in precapillary resistance which occur on standing, further compounding the problem of oedema formation\(^8\).

The COHORT study, undertaken in 828 elderly, hypertensive patients, reported that ankle oedema may have a delayed onset, with its incidence increasing gradually as treatment continues, meaning it is not likely to be a transient, self limiting effect\(^2,9\).

Ankle oedema in patients who have been taking CCBs for a long time may be associated with a petechial rash and in some cases hyper pigmentation and discolouration. This is thought to be due to increases in capillary permeability, leading to leakage of erythrocytes into the surrounding fluid\(^6,8\).

CCB-related oedema commonly worsens in the evening, and may resolve or improve following the patient lying down overnight\(^6\).

Differences in chemical class:
CCBs are generally classified into dihydropyridines (DHP) and non-dihydropyridines based on their chemical structure. Whilst ankle oedema is a class effect in all CCBs, there does appear to be differences in the incidence of ankle oedema between the different classes, with oedema more likely with the dihydropyridine agents\(^1,2,6,8\). The incidence of ankle oedema has been reported as ranging from 1-15% in patients treated with DHP agents\(^1\). Within the DHP group, it is thought that those which are more “membranophilic” (such as lercanidipine and lacidipine), may be associated with a lower incidence of ankle oedema\(^2\).
The rate of ankle oedema occurring with verapamil therapy is variable. Verapamil increases plasma volume whilst also reducing vasoconstriction in the lower extremities, similar to amlodipine and nifedipine\(^\text{10}\).

Some post-marketing surveillance data has reported a reduced incidence of ankle oedema in patients treated with diltiazem compared to other CCB agents\(^\text{6}\).

Ankle oedema also appears to be dose related, and its incidence may exceed 80% in patients taking long term high doses of DHP agents. However, this association may not occur in an exact dose-proportional relationship\(^\text{6,8}\).

Whilst the longer-acting CCBs generally appear to have fewer adverse effects associated with them (such as flushing, headache, and palpitations), this is not thought to be the case when considering ankle oedema\(^\text{5}\).

Differences in blood pressure lowering ability of different CCB agents do not seem to correlate with differences in ability to cause ankle oedema\(^\text{7}\).

**Reported Incidences:**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Source</th>
<th>Incidence of Ankle Oedema</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dihydropyridine CCBs</strong></td>
<td></td>
<td></td>
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<tr>
<td>Amlodipine</td>
<td>Summary of Product Characteristics (SPC)- Amlostin(^\text{11})</td>
<td>Common &gt;1/100 to &lt;1/10</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Andresdottir MB et al, 2000(^\text{5})</td>
<td>47%</td>
<td>N=32 Lower limb volume measured by water displacement- may have included clinically insignificant increases in foot volume. Funded by drug manufacturers.</td>
</tr>
<tr>
<td></td>
<td>Lombardo D et al 1994(^\text{5,12})</td>
<td>23%</td>
<td>Subjective reporting</td>
</tr>
<tr>
<td></td>
<td>Per Lund-Johansen 2003(^\text{7})</td>
<td>33.3%</td>
<td>N= 44 Postmenopausal hypertensive patients. Other possible causes of oedema were excluded from the study population. Lower limb volume measured by water displacement- may have included clinically insignificant increases in foot volume.</td>
</tr>
<tr>
<td>Nifedipine</td>
<td>SPC- Adalat(^\text{13})</td>
<td>Common &gt;1/100 to &lt;1/10</td>
<td>Oedema- not specified into what type</td>
</tr>
<tr>
<td></td>
<td>Terry RW, 1982(^\text{14})</td>
<td>7.7%- general population 10.3% in CHF subgroup 8.2% in concomitant beta blocker therapy subgroup 11.6%- long term therapy subgroup.</td>
<td>Review of 3081 patients with angina pectoris.</td>
</tr>
<tr>
<td></td>
<td>Blankfield RP, 2005(^\text{10})</td>
<td>1.7-32%</td>
<td>Review of 7 papers</td>
</tr>
<tr>
<td></td>
<td>MATH and EXACT trials(^\text{8,15,16})</td>
<td>7.7% at 18 weeks and 8.1% at 20 weeks</td>
<td>XL formulation of nifedipine</td>
</tr>
</tbody>
</table>
| Felodipine  | SPC- Plendi\(^\text{17}\)                  | Very Common >1/10        | Peripheral oedema  
"As with other dihydropyridines dose dependent ankle swelling can occur in patients treated with felodipine. This results from precapillary vasodilation and is not related to generalised fluid
<table>
<thead>
<tr>
<th>Drug</th>
<th>Incidence</th>
<th>Type of Study</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lercanidine</td>
<td>Uncommon- (&gt;1/1000 &lt;1/100)</td>
<td>Peripheral oedema - not specified into what type</td>
<td></td>
</tr>
<tr>
<td>Per Lund-Johansen 2003</td>
<td>9.8%</td>
<td>N=48</td>
<td>Post menopausal hypertensive patients.</td>
</tr>
<tr>
<td>Isradipine</td>
<td>Very common (≥ 1/10)</td>
<td>Peripheral oedema - not specified into what type.</td>
<td></td>
</tr>
<tr>
<td>STOP-2 trial</td>
<td>25.5%</td>
<td>Randomised, open masked-endpoint trial</td>
<td></td>
</tr>
<tr>
<td>Blankfield RP, 2005</td>
<td>7.7-13.9%</td>
<td>Review of 2 trials</td>
<td></td>
</tr>
<tr>
<td>Lacidipine</td>
<td>Common&gt; 1/100, &lt;1/10</td>
<td>Oedema</td>
<td></td>
</tr>
<tr>
<td>Andresdottir MB et al, 2000</td>
<td>20%</td>
<td>N=30</td>
<td>Lower limb volume measured by water displacement - may have included clinically insignificant increases in foot volume. Funded by drug manufacturers.</td>
</tr>
<tr>
<td>Blankfield RP, 2005</td>
<td>6%</td>
<td>Review</td>
<td></td>
</tr>
<tr>
<td>Lindholm LH et al 1996</td>
<td>4%</td>
<td>Review (via Andresdottir)</td>
<td></td>
</tr>
<tr>
<td>Nimodipine</td>
<td>Not listed</td>
<td>Subjective reporting</td>
<td></td>
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</tbody>
</table>

### Summary

The potential to cause ankle oedema appears to exist for all calcium channel blocking agents, and is caused by increasing capillary pressure leading to leakage of fluids into the surrounding tissues. This occurs in spite of the diuretic nature of some CCB agents.

Ankle oedema appears to occur more frequently in CCBs from the DHP group, although some agents such as lacidipine and lercanidipine may cause it less frequently than nifedipine and amlodipine. Diltiazem, a non-DHP agent, seems to be associated with the lowest incidence of ankle oedema.

### Limitations

Reporting of ankle oedema may be subjective, and methods to detect oedema formation were...
variable in the trials assessed, from relying on patient self-reporting, to using water displacement methods. This variation in reporting methods may be responsible for the wide differences in reported incidence of ankle oedema. In addition, inter and intra patient variability in susceptibility may play a part in the likelihood of oedema formation, so despite reported differences, it is still impossible to predict which agent may precipitate oedema in individual patients.

Quality Assurance

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Date Prepared
13th May 2013

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Date of check
Original: 29th June 2011
Update: 11th July 2013

Search strategy
Embase
*Calcium channel blocking agent AND *Ankle edema
*Amlodipine AND *Ankle edema
*Nifedipine AND *Ankle edema
*Felodipine AND *Ankle edema
*Lercanidipine AND *Ankle edema
*Isradipine AND *Ankle edema
*Lacidipine AND *Ankle edema
*Nimodipine AND *Ankle edema
*Diltiazem AND *Ankle edema
*Verapamil AND *Ankle edema

Medline
*Calcium Channel Blockers AND *Edema
*Amlodipine AND *Edema
*Nifedipine AND *Edema
*Felodipine AND *Edema
Lercanidipine.af AND *Edema
*Isradipine AND *Edema
Lacidipine.af AND *Edema
*Nimodipine AND *Edema

eMC & Micromedex

References

17 Summary of Product Characteristics: Plendil 2.5mg, Plendil 5mg and Plendil 10mg (felodipine). Astra-Zeneca Pharmaceuticals. Accessed via http://www.medicines.org.uk/EMC/medicine/191/SPC/Plendil+2.5mg%2c+Plendil+5mg+and+Plendil+10mg/ on 13th May 2011 [last updated on the eMC: 16/08/2012]

