medSask
YOUR MEDICATION INFORMATION SERVICE
DRUG NEWS

Addressing Dihydropyridine Calcium Channel Blocker-Associated Peripheral Edema

Clinical Pearl:

If edema is bothersome to a patient on a dihydropyridine calcium channel blocker (DHP-CCB), it may be appropriate to do one or a combination of the following:

- add a renin angiotensin aldosterone system (RAAS) blocker
- increase RAAS blocker dose
- lower the dose of DHP-CCB
- discontinue the DHP-CCB
- substitute an alternative agent in place of the DHP-CCB

Background

DHP-CCBs are a class of drugs used both as monotherapy and in combination therapy for the treatment of hypertension and angina in several categories of patients. The agents include amlodipine, felodipine and nifedipine. A common side effect of these medications is peripheral edema of the lower extremities[1]; it is reported to occur in up to one-third of patients on DHP-CCBs.[2] The frequency of this side effect is dose-dependent and occurs more often from short-acting as opposed to long-acting formulations of the same drug.[1-3] The edema is less of a safety concern than an issue in terms of patient adherence.[1,2] Edema may cause discomfort and may even lead to patients' decisions to discontinue medication, leaving them with increased risk of hypertension-related complications, especially in those with chronic kidney disease.[4] Though the initial management idea may be to switch therapy to an alternative class of drugs, DHP-CCBs have been shown to reduce mortality and morbidity when combined with certain RAAS blockers.[5] RAAS blockers have been shown reduce DHP-CCB-induced edema by as much as 38%.[3] Furthermore, options may be more limited in certain patient groups, such as African American people, who do not benefit as much from agents like beta blockers and ACEIs.[6] Replacing the DHP-CCB may not be an ideal option.

What is the pharmacodynamic event taking place that precipitates this side effect?

Lower leg peripheral edema is the result of selective dilation of blood vessels. DHP-CCBs dilate the pre-capillary rather than post-capillary blood vessels.[1] These vessels are the arteries transporting blood from the heart to the lower limbs. DHP-CCBs do not dilate post-capillary blood vessels (veins), leaving the pressure in these vessels unchanged.[1] This produces unbalanced pressure as the resistance in the blood vessels *leaving* the lower limb is greater than the resistance in the blood vessels delivering blood *to* the lower limb. The result is an increase in the capillary blood pressure as blood pools in these vessels. As the peripheral pressure increases, fluid moves from the capillaries into the interstitial space, resulting in peripheral edema.[1]

Agents that block RAAS include ACEIs and angiotensin-2 receptor blockers (ARBs); while the direct renin inhibitor aliskiren also blocks RAAS, it has not been studied for use in management of peripheral edema. Because of their complementary effect at the peripheral blood vessels, ACEIs and ARBs cause post-capillary venous dilation, which helps resolve the pressure differences across the artery/capillary/vein pathway.[1]

How do we approach a patient who presents with edema while taking a DHP-CCB?

The first step is to rule out other possible causes of edema. Though it may seem obvious the edema is due to the medication, it is important to remember there are several causes of edema. Other potential culprits should be considered including, but not limited to, use of other medications (e.g. NSAIDs), lifestyle changes (e.g. increased water and salt intake), development or exacerbation of other medical conditions (e.g. heart failure), and others, including medications.[2] (See Tables 1 & 2)

Table 1: Some Causes of Peripheral Edema[2]		
↑Capillary Hydrostatic Pressure		**↑Capillary Permeability**
Regional venous HTN	*↑plasma volume*	allergic reactions
deep vein thrombosis	heart failure	burns
chronic venous insufficiency	renal failure	inflammation/local infections
compartment syndrome	drugs	**Other**
Systemic venous HTN	pregnancy	medications (see Table 2)
heart failure	premenstrual edema	idiopathic
tricuspid valvular disease	**Lymphatic Obstruction**	myxedema
cirrhosis/liver failure	lymphedema	
↓Plasma Oncotic Pressure		
↓protein synthesis	*Protein loss*	
cirrhosis/liver failure	malabsorption	
malnutrition	preeclampsia	
malabsorption	nephrotic syndrome	

Table 2: Some Potential Medications that can Cause Peripheral Edema[2]	
α-adrenergic antagonists	**Hormones**
Antidepressants	*corticosteroids*
monoamine oxidase inhibitors	*erythropoietic agents*
Antihypertensives	*estrogens*
DHP-CCBs	*progestogens*
direct vasodilators – hydralazine, minoxidil	*testosterone*
beta-blockers	**Nonsteroidal anti-inflammatory agents**
centrally acting agents – clonidine, methyldopa	*non-selective cyclooxygenase inhibitors*
Antirheumatic drugs	*selective cyclooxygenase-2 inhibitors*
Chemotherapeutic drugs	**Pregabalin**
Endothelin receptor antagonists	**Thiazolidinediones**
ambrisentan	*pioglitazone*
bosentan	*rosiglitazone*

Once satisfied that the most probable cause of the edema is the DHP-CCB, we can start to look at possible therapy modifications. Start by assessing the patient's blood pressure, extent of the edema, and the discomfort to /concern of the patient. If the patient isn't bothered by this side effect, DHP-CCB therapy can be continued as long as the blood pressure targets are being met. In all cases of peripheral edema, non-pharmacological interventions should be initiated. Such interventions may include salt reduction, dosing at bedtime, limb elevation, and compression stockings.[2,7] If the patient is concerned about the edema, or if the edema is also accompanied by out-of-range high blood pressure values, consider changing the current regimen. In cases where blood pressure is on target but the edema is bothersome to the patient, the preferred option in most is to reduce the current dose of DHP-CCB therapy and introduce a RAAS blocker. If blood pressure targets are not met in addition to the edema, the dose of the DHP-CCB can remain as it were, while adding a RAAS-blocker.[2]

What if the edema persists despite introduction or current use of a RAAS-blocker?

If the patient's blood pressure is at target while on a combination of DHP-CCB and RAAS-blocker and the edema is still present, the best option is to increase the dose of RAAS-blocker and reduce the dose of the DHP-CCB, depending on blood pressure changes.[3] If the patient's blood pressure goals are still not met, the next course of action is to increase the RAAS-blocker dose and then re-evaluate. Decrease the DHP-CCB dose thereafter if the change induces hypotension. It is best to modify one component at a time and assess after

each adjustment in order to titrate therapy to the best individualized combination for that particular patient. If edema continues to be an issue despite increasing the RAAS-blocker as well as decreasing the DHP-CCB, it may be most appropriate to discontinue the DHP-CCB altogether, potentially substituting with an agent from an alternative drug class.[2]

Conclusion

The occurrence of peripheral edema from use of DHP-CCBs does not necessarily require discontinuation or even adjustment of the CCB, depending on BP values and patient satisfaction. RAAS-blocker therapy can be introduced to those patients whose BP goals are not met and/or find the edema bothersome. Dose adjustment of these agents may subsequently be required. It is important to look at patients individually when making decisions about therapy, paying particular attention to comorbidities and other medications.

Written by Jessica Morris, Pharmacy Intern
Reviewed by Karen Jensen MSc, BSP and Carmen Bell BSP
03 Apr 2017

References:

1. de la Sierra A. Mitigation of calcium channel blocker-related oedema in hypertension by antagonists of the renin–angiotensin system. J Hum Hypertens. 2009;23(8):503-511.
2. Epstein B, Roberts M. Managing peripheral edema in patients with arterial hypertension. Am J Ther. 2009;16(6):543-553.
3. Makani H, Bangalore S, Romero J, et al. Effect of renin-angiotensin system blockade on calcium channel blocker-associated peripheral edema. Am J Med. 2011;124(2):128-135.
4. DynaMed [Internet]. Ipswich (MA): EBSCO Information Services. 1995 - 2017. Record No. 115500, Hypertension management and use of antihypertensive medication in patients with chronic kidney disease; [updated 21 Apr 2016, cited 10 Mar 2017]; [about 25 screens]. Available from http://search.ebscohost.com/login.aspx?direct=true&db=dnh&AN=115500&site=dynamed-live&scope=site. Registration and login required.
5. American Society of Health System Pharmacists, Inc., DynaMed [Internet]. Ipswich (MA): EBSCO Information Services. 1995 - 2017. Record No. 233427, Amlodipine; [updated 19 Jan 2016 Jan 19; cited 10 Mar 2017]; [about 20 screens]. Available from http://search.ebscohost.com/login.aspx?direct=true&db=dnh&AN=233427&site=dynamed-live&scope=site. Registration and login required.
6. Flack J, Nasser S, Levy P. Therapy of hypertension in African Americans. Am J Cardiovasc Drugs. 2011; 11(2), 83-92.
7. Regier L, Jensen B. Calcium channel blocker (CCB): comparison chart. RxFiles. 10th ed. Saskatoon, SK: Saskatoon Health Region. [updated 01 Mar 2017; accessed 30 Mar 2017]. Available from: www.RxFiles.ca