

Therapeutic Class Overview

Calcium Channel Blocking Agents (Non-Dihydropyridines)

INTRODUCTION

- Approximately 92.1 million American adults have at least 1 type of cardiovascular disease according to the American Heart Association Heart Disease and Stroke Statistics 2017 update (Benjamin et al, 2017). From 2004 to 2014, mortality associated with cardiovascular disease declined 25.3%.
- Calcium channel blockade has certain effects that are specific to cardiac function. Coronary vascular smooth muscle relaxes when calcium channels are blocked which increases the flow of oxygenated blood into the myocardium and lowers coronary vascular resistance. In addition, calcium channel blocking agents (also called calcium channel blockers) decrease peripheral vascular resistance by relaxing arteriolar smooth muscle. Both coronary and systemic vasodilation serve to reduce cardiac workload (Kannam et al, 2017; Dobesh PP, 2017; Michel T, 2011).
- The movement of calcium ions is essential for the function of all types of muscle, including cardiac muscle and vascular smooth muscle. For both cardiac and smooth muscle, the flow of calcium ions into the muscle cells through specific channels allows muscle contraction to occur. When this flow is reduced, the result is a weakening of muscle contraction and relaxation of muscle tissue (Micromedex[®] 2.0, 2017; Kannam et al, 2017).
- The calcium channel blocking agents include dihydropyridines, which are similar in chemical structure, and non-dihydropyridines, which are a structurally heterogeneous group. Although they have different binding sites on the L-type calcium channel, both block the transmembrane influx of calcium ions into cardiac and vascular smooth muscle. The non-dihydropyridines also block the T-type calcium channel in the atrioventricular node (Micromedex 2.0, 2017; Kannam et al, 2017; Dobesh PP, 2017; Michel T, 2011; Saseen, 2017).
- The non-dihydropyridine calcium channel blocking agents include diltiazem and verapamil and both agents are available in a variety of modified-release delivery systems that alter their pharmacokinetic properties, including onset and duration of action (Micromedex 2.0, 2017). Non-dihydropyridines dilate the arteries somewhat less than dihydropyridines, but they also reduce heart rate and contractility (Micromedex 2.0, 2017; Kannam et al, 2017; Weber et al, 2014).
- The non-dihydropyridine calcium channel blocking agents are indicated for use in the treatment of angina, arrhythmias and hypertension. Diltiazem is a potent coronary vasodilator but is only a mild arterial vasodilator. Although it decreases atrioventricular (AV) node conduction, diltiazem does not have negative inotropic properties. Verapamil dilates coronary and peripheral arteries. It also slows conduction through the AV node and has negative inotropic and chronotropic effects (Micromedex 2.0, 2017).
- Guidelines stipulate that a non-dihydropyridine calcium channel blocker may be prescribed in certain patients, often with co-morbid indications. Non-dihydropyridine calcium-channel blocking agents are not recommended for the routine treatment of heart failure because of their negative inotropic action and risk of worsening heart failure (Yancy et al, 2013; Yancy et al, 2016; Yancy et al, 2017). Caution is also advised in elderly patients (American Geriatrics Society, 2015). Guidelines generally reserve non-dihydropyridine calcium channel blockers for patients with high risk cardiovascular diseases and arrhythmias; therefore, they are usually reserved for progressive cardiovascular and heart disease (American Geriatrics Society, 2015; Amsterdam et al, 2014; Fihn et al, 2014; Go et al, 2014; James et al, 2014; January et al, 2014; KDIGO, 2012; Mancina et al, 2013; Montalescot et al, 2013; Page et al, 2016; Rosendorff et al, 2015; Weber et al, 2014).
- Both the non-dihydropyridine calcium channel blocking agents, diltiazem and verapamil, are available generically in at least 1 formulation (Drugs@FDA.com, 2017; Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations, 2017).
- This review will focus on the non-dihydropyridine calcium channel blocking agents which are Food and Drug Administration (FDA) approved to treat hypertension, atrial fibrillation and flutter, and chronic stable angina. Verapamil is also FDA-approved for unstable angina and variant angina indications. Since there are several branded agents that contain the same generic component, the remaining tables in the review are organized by generic name. Covera-HS (verapamil extended-release) is not included in this review as it has been discontinued by the manufacturer. This review encompasses all dosage forms, and strengths with the exception of injectable indications and formulations used primarily in an institutional setting.
- Medispan Therapeutic Class: Calcium Channel Blockers

Table 1. Medications Included Within Class Review

| Drug | Generic Availability |
|---|----------------------|
| Calan (verapamil) tablet | ✓ |
| Calan SR (verapamil extended-release) tablet | ✓ |
| Cardizem (diltiazem) tablet | ✓ |
| Cardizem CD* (diltiazem extended-release) capsule | ✓ |
| Cardizem LA† (diltiazem extended-release) tablet | ✓ |
| Dilacor XR‡ (diltiazem extended-release) capsule | ✓ |
| Tiazac§ (diltiazem extended-release) capsule | ✓ |
| Verelan (verapamil sustained-release) capsule | ✓ |
| Verelan PM (verapamil extended-release) capsule | ✓ |

*Cartia XT is a branded generic of Cardizem CD.

†Matzim LA is the branded generic of Cardizem LA.

‡Dilacor XR is no longer manufactured, but included in this review because its branded generic, DILT-XR, is still on the market.

§Taztia XT is a branded generic of Tiazac.

(*Drugs @FDA 2017, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2017*)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

| Indication | Diltiazem | Verapamil |
|--|---|-----------|
| Angina Pectoris | | |
| Angina due to coronary artery spasm or vasospastic angina | ✓ (tablet [Cardizem], extended-release capsule [Cardizem CD]) | ✓ (Calan) |
| Chronic stable angina | ✓ | ✓ (Calan) |
| Unstable angina | - | ✓ (Calan) |
| Arrhythmias | | |
| Control of ventricular rate at rest and during stress in patients with chronic atrial flutter and/or atrial fibrillation in association with digitalis | - | ✓ (Calan) |
| Prophylaxis of repetitive paroxysmal supraventricular tachycardia | - | ✓ (Calan) |
| Hypertension | | |
| Hypertension | ✓ *(with the exception of Cardizem) | - |
| Hypertension to lower blood pressure which reduces the risk of fatal and nonfatal cardiovascular events, primarily strokes and myocardial infarctions. | ✓ *(Cardizem LA) | ✓ |

*May be used alone or in combination with other antihypertensive agents.

(Prescribing Information: CALAN, 2016; CALAN SR, 2016; CARDIZEM, 2016; CARDIZEM CD, 2016; CARDIZEM LA, 2016; DILT-XR, 2012; TIAZAC, 2016; VERELAN, 2016; VERELAN PM, 2016)

- Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

- The non-dihydropyridine calcium channel blockers are indicated to treat hypertension and angina, in addition to slowing ventricular rate in patients with atrial fibrillation/atrial flutter. Clinical trials demonstrate the efficacy of these agents for their respective indications.
- For the treatment of angina, diltiazem and verapamil have been shown to be effective in improving exercise tolerance and reducing heart rate, angina frequency and nitroglycerin use (De Rosa et al, 1998; Chugh et al, 2001; van Kesteren et al, 1998; Frishman et al, 1999).

- A direct comparison between diltiazem and verapamil found no significant differences between the agents in exercise tolerance; however, resting heart rate, angina frequency and nitroglycerin use were all significantly lower in the diltiazem group (De Rosa et al, 1998).
- Both diltiazem and verapamil have shown efficacy in the treatment of hypertension, but comparisons with other classes of medication have not consistently demonstrated “superiority” of either agent (Wright et al, 2004; Rosei et al, 1997).
 - Wright and colleagues compared diltiazem and amlodipine in African American patients with hypertension and demonstrated significantly greater reductions in diastolic blood pressure during the first 4 hours after awakening in addition to greater reductions in heart rate with diltiazem; however, mean 24-hour systolic blood pressure reductions were significantly greater with amlodipine (Wright et al, 2004).
- Studies evaluating the efficacy of the non-dihydropyridine calcium channel blockers for various cardiovascular outcomes generally demonstrated no significant difference between verapamil or diltiazem compared to other agents including beta blockers and diuretics (Hansson et al, 2000; Pepine et al, 2003; Mancina et al, 2007; Bangalore et al, 2008; Black et al, 2003).

CLINICAL GUIDELINES

- There are several national and international evidence-based antihypertensive guidelines that provide recommendations regarding the use of calcium channel blocking agents. Most recommend that the selection of an antihypertensive agent be based on compelling indications for use:
 - Most guidelines recommend a thiazide-type diuretic, an angiotensin-converting enzyme (ACE) inhibitor, an angiotensin II receptor blocker (ARB), or a calcium channel blocker as first-line therapy (Go et al, 2014; James et al, 2013; Mancina et al, 2013; Weber et al, 2014), although the 2013 European Society of Hypertension/European Society of Cardiology (ESH/ESC) guidelines also recommend beta blockers as a first-line therapy option (Mancina et al, 2013).
 - In black hypertensive patients, thiazide-type diuretics or calcium channel blockers are recommended specifically as first-line therapy (James et al, 2014; Mancina et al, 2013; Weber et al, 2014).
 - In patients with chronic kidney disease, calcium channel blockers are generally recommended after ACE inhibitors or ARBs (KDIGO, 2012; Go et al, 2014; James et al, 2014; Mancina et al, 2013; Weber et al, 2014).
 - There is no consensus on additional populations that calcium channel blockers should be prescribed in. However, other compelling indications that include calcium channel blockers as a first-line treatment option include elderly patients, patients with diabetes, for ventricular rate control in atrial fibrillation, patients with asymptomatic organ damage and asymptomatic atherosclerosis, peripheral artery disease, and metabolic syndrome (Go et al, 2014; James et al, 2014; KDIGO, 2012; Mancina et al, 2013; Weber et al, 2014). A non-dihydropyridine calcium channel blocker may be prescribed for hypertensive patients with coronary artery disease (CAD) who have an intolerance or contraindication to a beta blocker; however, a combination of a beta blocker and a non-dihydropyridine calcium channel blocker may increase the risk of bradyarrhythmias and heart failure (Rosendorff et al, 2015).
 - Non-dihydropyridine calcium-channel blocking agents are not recommended for the routine treatment of heart failure because of their negative inotropic action and risk of worsening heart failure (Yancy et al, 2013; Yancy et al, 2016; Yancy et al, 2017).

SAFETY SUMMARY

- Diltiazem is contraindicated in patients with i) acute myocardial infarction and pulmonary congestion documented by X-ray on admission, ii) hypersensitivity to the drug, iii) hypotension (< 90 mm Hg systolic), iv) second or third degree AV block except in the presence of a functioning ventricular pacemaker, and v) sick sinus syndrome except in the presence of a functioning ventricular pacemaker. Verapamil is contraindicated in patients with i) atrial fibrillation or flutter and an accessory bypass tract (Wolff-Parkinson-White, Lown-Ganong-Levine syndromes), ii) hypersensitivity to the drug, iii) hypotension (< 90 mm Hg systolic), iv) second or third degree AV block except in the presence of a functioning ventricular pacemaker, v) severe left ventricular dysfunction, and vi) sick sinus syndrome except in the presence of a functioning ventricular pacemaker.
- The precautions for diltiazem include the following: may have an additive effect on heart rate with concomitant use of beta blockers or digitalis; dermatologic reactions leading to erythema multiforme and/or exfoliative dermatitis have been reported; increased risk of toxicity with hepatic and/or renal impairment; hypotension; impaired ventricular function and worsening congestive heart failure have also been reported. The precautions for verapamil include the following: concomitant use of a beta blocker in patients with any degree of ventricular dysfunction and concomitant use of quinidine in patients with hypotrophic cardiomyopathy should be avoided; congestive heart failure may occur; elevated

liver enzymes, particularly serum transaminase levels, have been reported; first-degree AV block, marked, or progression to second- or third-degree block may occur; hepatic function impairment may occur; sinus bradycardia, pulmonary edema, severe hypotension, second-degree AV block, sinus arrest, and death have been reported in patients with hypertrophic cardiomyopathy; hypotension and/or dizziness may occur; pulmonary edema may occur.

- In general, patients taking non-dihydropyridine calcium channel blocking agents should have their blood pressure monitored weekly during the initial period of titration. Heart rate and anginal pain should also be monitored. Patients should have their liver function monitored periodically. Electrocardiogram (ECG) should be monitored for PR interval prolongation in patients with impaired renal or hepatic function using verapamil. If the medication is being used for arrhythmia, then ECG and reduction in signs and symptoms should be monitored.
- The common adverse effects of diltiazem include bradyarrhythmia, cough, dizziness, fatigue, headache and peripheral edema. The common adverse effects of verapamil include constipation, dizziness, edema, headache, hypotension, influenza-like symptoms, pharyngitis, and sinusitis.

(Micromedex 2.0, 2017).

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

| Drug | Available Formulations | Usual Recommended Frequency | Comments |
|-----------|--|---|---|
| Diltiazem | <p>Extended-release capsule: 60 mg 90 mg 120 mg 180 mg 240 mg 300 mg 360 mg 420 mg</p> <p>Extended-release tablet: 120 mg 180 mg 240 mg 300 mg 360 mg 420 mg</p> <p>Tablet: 30 mg 60 mg 90 mg 120 mg</p> | <p><u>Angina pectoris (chronic stable):</u> Extended-release capsule: initial, 120 or 180 mg once daily; maintenance, 180 to 540 mg once daily; maximum, 540 mg once daily</p> <p>Extended-release tablet: initial, 180 mg once daily; maximum, 360 mg once daily</p> <p>Tablet: initial, 30 mg 4 times daily; maintenance, 180 to 360 mg/day (divided in 3 to 4 doses)</p> <p><u>Angina pectoris (due to coronary artery spasm):</u> Extended-release capsule (Cardizem CD): initial, 120 or 180 mg once daily; maintenance, adjust dosage to each patient's needs up to 480 mg once daily</p> <p>Tablet: initial, 30 mg 4 times daily; maintenance, 180 to 360 mg/day (divided in 3 to 4 doses)</p> <p><u>Hypertension:</u> Extended-release capsule: initial, 120 to 240 mg once daily; maintenance, 120 to 540 mg once daily; maximum, 540 mg once daily</p> <p>Extended-release tablet: initial, 180 to 240 mg once daily, although some patients may respond to lower doses; maximum, 540 mg once daily</p> | <p>Tablet formulation should be taken before meals and at bedtime. Tiazac (extended-release) capsule formulation may also be administered by opening the capsule and sprinkling the capsule contents on a spoonful of applesauce; the applesauce should be swallowed immediately without chewing and followed with a glass of cool water to ensure complete swallowing of the capsule contents. Cardizem LA (extended-release) tablets should be swallowed whole and not chewed or crushed.</p> |

| Drug | Available Formulations | Usual Recommended Frequency | Comments |
|-----------|---|--|--|
| Verapamil | <p>Extended-release capsule: 100 mg 120 mg 180 mg 200 mg 240 mg 300 mg</p> <p>Extended-release tablet: 120 mg 180 mg 240 mg</p> <p>Sustained-release capsule: 120 mg 180 mg 240 mg 360 mg</p> <p>Tablet: 40 mg 80 mg 120 mg</p> | <p><u>Angina pectoris (chronic stable, unstable, and vasospastic):</u> Tablet: maintenance, 80 to 120 mg 3 times daily</p> <p><u>Arrhythmias:</u> Tablet: maintenance, 240 to 320 mg/day, divided in 3 to 4 doses; maximum, 480 mg/day</p> <p><u>Hypertension:</u> Sustained-release capsule: initial, 120 to 240 mg once daily; maintenance, 180 mg to 480 mg/day; maximum, 480 mg/day</p> <p>Extended-release capsule: initial, 100 mg to 200 mg once daily at bedtime; maintenance, 200 mg to 400 mg once daily; maximum, 400 mg/day</p> <p>Extended-release tablet: initial, 120 to 180 mg in the morning; maintenance, 180 to 480 mg/day in 1 to 2 divided doses, maximum, 480 mg/day</p> <p>Tablet: initial, 80 mg 3 times daily; maintenance, 360 to 480 mg/day divided (3 to 4 times daily); maximum, 480 mg/day</p> | <p>Calan 80 mg tablets are scored and can be divided into halves to provide a 40 mg dose. Calan SR should be administered with food and if needed the caplets can be divided in half without compromising the sustained-release properties of the drug. Verelan and Verelan PM capsules should not be crushed or chewed and they may be administered by opening the capsule and sprinkling the capsule contents on a spoonful of applesauce; the applesauce should be swallowed immediately without chewing and followed with a glass of cool water to ensure complete swallowing of the capsule contents.</p> |

See the current prescribing information for full details

CONCLUSION

- The non-dihydropyridine calcium channel blocking agents are approved for the treatment of angina, arrhythmias, and hypertension. Diltiazem and verapamil are available in a variety of modified-release delivery systems that alter their pharmacokinetic properties, including onset and duration of action.
 - Both drugs are available in a generic formulation.
- Clinical trials demonstrate that diltiazem and verapamil can effectively treat angina and improve blood pressure (De Rosa et al, 1998; Chugh et al, 2001; van Kesteren et al, 1998; Frishman et al, 1999; Hauf-Zachariou et al, 1997; Wright et al, 2004; White et al, 2004; Rosei et al, 1997; Ruggenenti et al, 2004; Messerli et al, 2007; Karlberg et al, 2000; Van Bortel et al, 2008; Hilleman et al, 1999; Casas et al, 2005). Both agents have been shown to reduce mortality and cardiovascular event rates compared to placebo (Gibson et al, 2000). Evidence suggests that there is no overall difference between diltiazem and verapamil compared to other antihypertensive agents (beta blockers, diuretics) in reducing cardiovascular events and mortality in patients with hypertension (Hansson et al, 2000; Pepine et al, 2003; Mancia et al, 2007; Pepine et al, 2006; Bangalore et al, 2008; Brunner et al, 2007; Black et al, 2003).
- There is insufficient evidence to support that one non-dihydropyridine calcium channel blocking agent is safer or more efficacious than another.
- For the treatment of chronic angina, beta blockers are recommended as initial therapy; however, long-acting calcium-channel blocking agents may be used if beta blockers are contraindicated or if additional therapy is required (Fihn et al, 2012; Fihn et al, 2014; O’Gara et al, 2013; Montalescot et al, 2013). Beta blockers and calcium channel blockers have similar clinical outcomes, but beta blockers may have fewer adverse events in patients with stable angina. Long-acting calcium channel blockers may be used in combination with beta blockers when beta blocker monotherapy is

unsuccessful (Montalescot et al, 2013; Amsterdam et al, 2014). Long-acting calcium-channel blocking agents are also recommended in patients with variant angina and for patients with coronary artery spasm(s), known as vasospastic angina, with or without nitrates (Montalescot et al, 2013; Amsterdam et al, 2014).

- Treatment options for atrial fibrillation include ventricular rate control or drug therapy to maintain sinus rhythm. The AFFIRM, RACE and HOT CAFE trials demonstrated similar outcomes with rate control compared to rhythm control strategies. Beta blockers or non-dihydropyridine calcium channel blockers are recommended for patients with persistent, paroxysmal, or permanent atrial fibrillation; however, in patients with decompensated heart failure or pre-excitation and atrial fibrillation, non-dihydropyridine calcium channel blockers should not be administered (January et al, 2014). Propafenone or flecainide (“pill-in-the-pocket”) in combination with a beta blocker or non-dihydropyridine calcium channel blocker are options to terminate atrial fibrillation outside of a hospital for select patients. Non-dihydropyridine calcium channel blockers may also be prescribed as monotherapy or in combination with other treatment in patients with atrial fibrillation and co-morbid hypertrophic cardiomyopathy, certain acute coronary syndrome patients, or chronic obstructive pulmonary disease (January et al, 2014). In cases of ventricular and supraventricular arrhythmias, intravenous non-dihydropyridine calcium channel blockers are recommended (Zipes et al, 2006; Page et al, 2016). Oral non-dihydropyridine calcium channel blockers may be used for the chronic management of patients with symptomatic supraventricular tachycardia without ventricular excitation (Page et al, 2016).
- Caution is advised with use in elderly patients with systolic heart failure; non-dihydropyridine calcium channel blockers have the potential to promote fluid retention and/or exacerbate heart failure (American Geriatrics Society, 2015).

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Publication Date: Month DD, YYYY