Review Article

# A Review on Phenyl Alkylamine Class of Drug; Verapamil

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**ABSTRACT**

Current therapies those alleviate angina frequency and increase the threshold at which demand-induced myocardial ischemic symptoms become evident include drugs (nitrates, β-blockers, calcium antagonists), exercise conditioning, enhanced external counter pulsation, and coronary revascularization. Verapamil is the prototype of those agents which selectively inhibit membrane transport of calcium, an action which accounts for the drug's peripheral and coronary vasodilator properties, its effect on excitation-contraction coupling and hence its negative inotropic propensity, as well as its depressant effects on the sinus node and atrioventricular conduction. Its pharmacological effects are largely independent of the autonomic nervous system. The main therapeutic uses of the drug are in the management of atrial tachyarrhythmias, angina, and possibly hypertension. This review will focus on verapamil, a phenyl alkyl amine class of drug which inhibit the calcium channel and there by reducing the chances of hypertension and angina pectoris.

**Keywords:** Verapamil, Angina pectoris, Hypertension.

## INTRODUCTION

Verapamil is a novel antiarrhythmic and antianginal agent which, although introduced in 1962, has only recently gained prominence not only as a significant agent in cardiovascular therapeutics but also as a powerful tool to examine the nature of some of the biophysical phenomena at the membrane of cardiac and other excitable tissues. Verapamil is the prototype of those agents which selectively inhibit membrane transport of calcium, an action which accounts for the drug's peripheral and coronary vasodilator properties, its effect on excitation-contraction coupling and hence its negative inotropic propensity, as well as its depressant effects on the sinus node and atrioventricular conduction. Its pharmacological effects are largely independent of the autonomic nervous system. The main therapeutic uses of the drug are in the management of atrial tachyarrhythmias, angina, and possibly hypertension. The overall experimental and clinical data suggest that verapamil will become an important and safe addition to existing drug regimens, especially as an agent of choice for the short-term treatment of most cases of paroxysmal supraventricular tachycardias. The initial experience in other arrhythmias, angina and hypertension, is also sufficiently encouraging to justify further detailed clinical trials to define its potential role in cardiovascular therapeutics[1]

Angina pectoris is chest pain ascribable to ischemia (a lack of blood, thus a lack of oxygen supply and waste removal) of the heart muscle, generally due to obstruction or spasm of the coronary arteries. Coronary artery disease, the principal cause of angina, is due to atherosclerosis of the cardiac arteries. The term descends from the Latin angina ("infection of the throat"), the Greek ankhonē ("strangling"), and the Latin pectus ("chest"), and can therefore be translated as "a strangling feeling in the chest". There is a feeble relationship between severity of pain and degree of oxygen deprivation in the heart muscle. There can be severe pain with little or no risk of a heart attack, and on the otherhand heart attack can occur without pain. Worsening ("crescendo") angina attacks, sudden-onset angina at rest, and angina lasting more than 15 minutes are symptoms of unstable

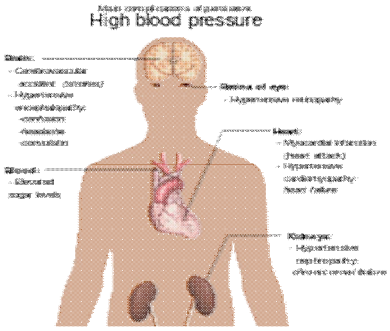
angina (usually grouped with similar conditions as the acute coronary syndrome). As these may herald myocardial infarction (a heart attack), they require urgent medical attention and are generally treated as a presumed heart attack.[2]

Hypertension (HTN) or high blood pressure, sometimes called arterial hypertension, is a chronic medical condition in which the blood pressure in the arteries is elevated. This requires the heart to work harder than normal to circulate blood through the blood vessels. Blood pressure involves two measurements, systolic and diastolic, which depend on whether the heart muscle is contracting (systole) or relaxed between beats (diastole). Normal blood pressure at rest is within the range of 100-140mmHg systolic (top reading) and 60-90mmHg diastolic (bottom reading). High blood pressure is said to be present if it is persistently at or above 140/90 mmHg.

Hypertension is classified as either primary (essential) hypertension or secondary hypertension; about 90–95% of cases are categorized as "primary hypertension" which means high blood pressure with no obvious underlying medical cause. The remaining 5–10% of cases (secondary hypertension) are caused by other conditions that affect the kidneys, arteries, heart or endocrine system.

Hypertension is a major risk factor for stroke, myocardial infarction (heart attacks), heart failure, aneurysms of the arteries (e.g. aortic aneurysm), peripheral arterial disease and is a cause of chronic kidney disease. Even moderate elevation of arterial blood pressure is associated with a shortened life expectancy. Dietary and lifestyle changes can improve blood pressure control and decrease the risk of associated health complications, although drug treatment is often necessary in people for whom lifestyle changes prove ineffective or insufficient.[3]

Complications of hypertension




Hypertension is diagnosed on the basis of a persistently high blood pressure. Traditionally, this requires three separate sphygmomanometer measurements at one monthly intervals. Initial assessment of the hypertensive people should include a complete history and physical examination. With the availability of 24-hour ambulatory blood pressure monitors and home blood pressure machines, the importance of not wrongly diagnosing those who have white coat hypertension has led to a change in protocols. In the United Kingdom, current best practice is to follow up a single raised clinic reading with ambulatory measurement, or less ideally with home blood pressure monitoring over the course of 7 days.

Secondary hypertension is more common in preadolescent children, with most cases caused by renal disease. Primary or essential hypertension is more common in adolescents and has multiple risk factors, including obesity and a family history of hypertension. Laboratory tests can also be performed to identify possible causes of secondary hypertension, and to determine whether hypertension has caused damage to the heart, eyes, and kidneys. Additional tests for diabetes and high cholesterol levels are usually performed because these conditions are additional risk factors for the development of heart disease and require treatment[4].

Serum creatinine is measured to assess for the presence of kidney disease, which can be either the cause or the result of hypertension. Serum creatinine alone may overestimate glomerular filtration rate and recent guidelines advocate the use of predictive equations such as the Modification of Diet in Renal Disease (MDRD) formula to estimate glomerular

filtration rate (eGFR). eGFR can also provides a baseline measurement of kidney function that can be used to monitor for side effects of certain antihypertensive drugs on kidney function. Additionally, testing of urine samples for protein is used as a secondary indicator of kidney disease. Electrocardiogram (EKG/ECG) testing is done to check for evidence that the heart is under strain from high blood pressure. It may also show whether there is thickening of the heart muscle (left ventricular hypertrophy) or whether the heart has experienced a prior minor disturbance such as a silent heart attack. A chest X-ray or an echocardiogram may also be performed to look for signs of heart enlargement or damage to the heart.

**Prevention**

Much of the disease burden of high blood pressure is experienced by people who are not labelled as hypertensive. Consequently, population strategies are required to reduce the consequences of high blood pressure and reduce the need for antihypertensive drug therapy. Lifestyle changes are recommended to lower blood pressure, before starting drug therapy. The British Hypertension Society guidelines[5] proposed the following lifestyle changes consistent with those outlined by the US National High BP Education Program in 2002 for the primary prevention of hypertension:

- Maintain normal body weight for adults (e.g. body mass index 20–25 kg/m$^2$)
- Reduce dietary sodium intake to <100 mmol/ day (<6 g of sodium chloride or <2.4 g of sodium per day)
- Engage in regular aerobic physical activity such as brisk walking (≥30 min per day, most days of the week)
- Limit alcohol consumption to no more than 3 units/day in men and no more than 2 units/day in women
- Consume a diet rich in fruit and vegetables (e.g. at least five portions per day);
- Consume a diet with reduced content of saturated and total fat.

Effective lifestyle modification may lower blood pressure as much an individual antihypertensive drug. Combinations of two or more lifestyle modifications can achieve even better results[6].

**Management**

**Lifestyle modifications**

The first line of treatment for hypertension is identical to the recommended preventative lifestyle changes and includes: dietary changesphysical exercise, and weight loss. These have all been shown to significantly reduce blood pressure in people with hypertension. If hypertension is high enough to justify immediate use of medications, lifestyle changes are still recommended in conjunction with medication. Different programs aimed to reduce psychological stress such as biofeedback, relaxation or meditation are advertised to reduce hypertension. However, in general claims of efficacy are not supported by scientific studies, which have been in general of low quality[7].

Dietary change such as a low sodium diet is beneficial. A long term (more than 4 weeks) low sodium diet in Caucasians is effective in reducing blood pressure, both in people with hypertension and in people with normal blood pressure[8]. Also, the DASH diet, a diet rich in nuts, whole grains, fish, poultry, fruits and vegetables promoted by the National Heart, Lung, and Blood Institute lowers blood pressure. A major feature of the plan is limiting intake of sodium, although the diet is also rich in potassium, magnesium, calcium, as well as protein[9].

**Medications**

Several classes of medications, collectively referred to as antihypertensive drugs, are currently available for treating hypertension. Prescription should take into account the person's cardiovascular risk (including risk of myocardial infarction and stroke) as well as blood pressure readings, in order to gain a more accurate picture of the person's cardiovascular profile[10]. If drug treatment is initiated the National Heart, Lung, and Blood Institute's Seventh Joint National Committee on High Blood Pressure (JNC-7) recommends that the physician not only monitor for response to treatment but should also assess for any adverse reactions resulting

from the medication. Reduction of the blood pressure by 5 mmHg can decrease the risk of stroke by 34%, of ischaemic heart disease by 21%, and reduce the likelihood of dementia, heart failure, and mortality from cardiovascular disease[11.] The aim of treatment should be to reduce blood pressure to <140/90 mmHg for most individuals, and lower for those with diabetes or kidney disease (some medical professionals recommend keeping levels below 120/80 mmHg). If the blood pressure goal is not met, a change in treatment should be made as therapeutic inertia is a clear impediment to blood pressure control[12].

Guidelines on the choice of agents and how to best to step up treatment for various subgroups have changed over time and differ between countries. The best first line agent is disputed[13]. The Cochrane collaboration, World Health Organization and the United States guidelines supports low dose thiazide-based diuretic as first line treatment[14]. The UK guidelines emphasise calcium channel blockers (CCB) in preference for people over the age of 55 years or if of African or Caribbean family origin, with angiotensin converting enzyme inhibitors (ACE-I) used first line for younger people. In Japan starting with any one of six classes of medications including: CCB, ACEI/ARB, thiazide diuretics, beta-blockers, and alpha-blockers is deemed reasonable while in Canada all of these but alpha-blockers are recommended as options[15-17].

**Drug combinations**

The majority of people require more than one drug to control their hypertension. JNC7 and ESH-ESC guidelines advocate starting treatment with two drugs when blood pressure is >20 mmHg above systolic or >10 mmHg above diastolic targets. Preferred combinations are renin–angiotensin system inhibitors and calcium channel blockers, or renin–angiotensin system inhibitors and diuretics[18]. Acceptable combinations include calcium channel blockers and diuretics, beta-blockers and diuretics, dihydropyridine calcium channel blockers and beta-blockers, or dihydropyridine calcium channel blockers with either verapamil or diltiazem. Unacceptable combinations are non-dihydropyridine calcium blockers (such as verapamil or diltiazem) and beta-blockers, dual renin–angiotensin system blockade (e.g. angiotensin converting enzyme inhibitor + angiotensin receptor blocker), renin–angiotensin system blockers and beta-blockers, beta-blockers and anti-adrenergic drugs[19]. Combinations of an ACE-inhibitor or angiotensin II–receptor antagonist, a diuretic and an NSAID (including selective COX-2 inhibitors and non-prescribed drugs such as ibuprofen) should be avoided whenever possible due to a high documented risk of acute renal failure. The combination is known colloquially as a "triple whammy" in the Australian health industry[20]. Tablets containing fixed combinations of two classes of drugs are available and while convenient for the people, may be best reserved for those who have been established on the individual components.

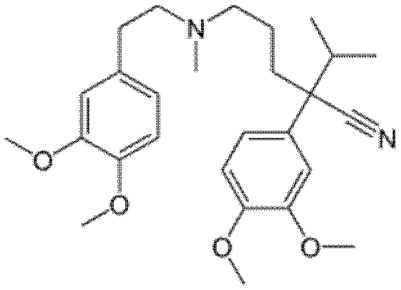
**Treatment for Angina**

The goals of treatment are to alleviate the frequency of angina, increase longevity, and improve patient's quality of life. Management of risk factors is an essential component of this therapy. The three classes of drugs commonly used for chronic angina include β adrenergic blocking agents, calcium channel blockers, and short- and long-acting nitrates. Each of these drug classes decreases cardiac workload and may increase coronary blood flow or improve its distribution and thus modify the imbalance between myocardial supply and demand. Although monotherapy is effective in some, the majority of patients require two or more antianginal agents to control their symptoms[21]. The choice of first-line treatment remains controversial because no single class of drug has demonstrated unequivocal superiority. Long-acting nitrates, β-adrenergic blocking agents, and calcium channel blockers, either alone or in combination, have been proven effective in reducing the frequency of angina. Sublingual nitroglycerin relieves episodes of angina and is also effective for short-term prophylaxis. The effectiveness of oral nitrates or transdermal preparations is

limited by the development of tolerance to their hemodynamic, antianginal, and anti-ischemic effects when administered in a dosing strategy designed to provide therapeutic plasma nitrate levels throughout 24 hours each day. In the absence of contraindications, β blockers are recommended as first-line treatment by the American Heart Association/American College of Cardiology guidelines particularly in patients with a previous myocardial infarction because reduced mortality has been demonstrated in such cases[22].Calcium channel blockers may be associated with unwanted side effects in angina patients with heart failure or abnormal left ventricular systolic function[38]. For example, the Multicenter Diltiazem post-infarction trial findings suggest that in patients with left ventricular dysfunction, diltiazem increased the frequency of late-onset heart failure and cardiac events. Whereas long-acting preparations have been better tolerated, flushing, headache, constipation, and peripheral edema continue to be problematic. The rate-lowering calcium channel blockers may also cause excessive bradycardia and heart block[23].

**Drug profile**

verapamil



Chemical formula-$C_{27}H_{38}N_2O_4$ , Chemical IUPAC Name- (*RS*)-2-(3,4-dimethoxyphenyl)-5-{[2-(3,4- dimethoxy phenyl) ethyl]- (methyl)amino} -2- prop-2-yl pentane nitrile**,** Molecular Weight 491.08g/mol

**Mechanism of action**

Verapamil inhibits voltage-dependent calcium channels. Specifically, its effect on L-type calcium channels in the heart causes a reduction in ionotropy and chronotropy, thuis reducing heart rate and blood pressure[37]. The pain of angina is caused by a deficit in oxygen supply to the heart. Calcium channel blockers like Verapamil will dilate blood vessels, which increases the supply of blood and oxygen to the heart. This controls chest pain, but only when used regularly[24].

**Clinical pharmacology and pharmacokinetics**

Given orally, 90–100% of Verapamil is absorbed, but due to high first-pass metabolism, bioavailability is much lower (10–35%). It is 90%bound to plasma proteins and has a volume of distribution of 3–5 L/kg. It is metabolized in the liver to at least 12 inactive metabolites (though one metabolite, norverapamil, retains 20% of the vasodilating activity of the parent drug). As its metabolites, 70% is excreted in the urine and 16% in feces; 3–4% is excreted unchanged in urine. This is a non-linear dependence between plasma concentration and dosage.[25,30,31].

Onset of action is 1–2 hours after oral dosage. Half-life is 5–12 hours (with chronic dosages). It is not cleared by hemodialysis. It is excreted in human milk. Because of the potential for adverse reaction in nursing infants from Verapamil, nursing should be discontinued while Verapamil is administered[32,33].

Verapamil has been reported to be effective in both short-term and long-term treatment of mania and hypomania. Addition ofmagnesium oxide to the verapamil treatment protocol enhances the antimanic effect. It has on occasion been used to control mania in pregnant patients, especially in the first 3 months[34,35]. It does not appear to be significantly teratogenic. For this reason, when one wants to avoid taking valproic acid (which is high in teratogenicity) or lithium (which has a small but significant incidence of causing cardiac malformation), Verapamil is usable as an alternative, albeit presumably a less effective one[26, 36].

**Side Effects**

Some possible side effects of the drug are headaches, facial flushing, dizziness, lightheadedness, swelling, increased urination, fatigue, nausea, ecchymosis, galactorrhea, and constipation. Along with other calcium channel blockers, verapamil is known to induce gingival hyperplasia[27].

**Overdose**

Acute overdose is often manifested by nausea, asthenia, bradycardia, dizziness, hypotension and cardiac arrhythmia. Plasma, serum or blood concentrations of verapamil and norverapamil, its major active metabolite, may be measured to confirm a diagnosis of poisoning in hospitalized patients or to aid in the medicolegal investigation of fatalities. Blood or plasma verapamil concentrations are usually in a range of 50-500 µg/L in persons on therapy with the drug, but may rise to 1–4 mg/L in acute overdose patients and are often at levels of 5–10 mg/L in fatal poisonings[28].

**Contraindication**

Severe left ventricular dysfunction, Hypotension, cardiogenic shock, Sick sinus syndrome, Second-or third-degree AV block, Patients with atrial flutter or atrial fibrillation and an accessory bypass tract or Patients with known hypersensitivity to verapamil hydrochloride[29].

**Drug interaction**

- Cytochrome inducers/inhibitors: Clinically significant interactions have been reported with inhibitors of CYP3A4 (e.g., erythromycin, ritonavir) causing elevation of plasma levels of verapamil while inducers of CYP3A4 (e.g., rifampin) have caused a lowering of plasma levels of verapamil.
- HMG-CoA reductase inhibitors: The use of HMG-CoA reductase inhibitors that are CYP3A4 substrates in combination with verapamil has been associated with reports of myopathy/ rhabdomyolysis[39].
- Co-administration of multiple doses of 10 mg of verapamil with 80 mg simvastatin resulted in exposure to simvastatin 2.5-fold that following simvastatin alone[40].
- Aspirin: In a few reported cases, co-administration of verapamil with aspirin has led to increased bleeding times greater than observed with aspirin alone.
- Grapefruit juice: Grapefruit juice may increase plasma levels of verapamil.
- Alcohol: Verapamil may increase blood alcohol concentrations and prolong its effects

**CONCLUSION**

Verapamil is a calcium channel antagonist. It inhibits the calcium channel present in the heart and further it will decrease the heart rate there by reducing the force of contraction and prevent heart failure, acute and chronic myocardial ischemia, ventricular and supraventricular arrhythmias.. Verapamil has been reported to be effective in both short-term and long-term treatment of mania and hypomania. Addition ofmagnesium oxide to the verapamil treatment protocol enhances the antimanic effect. It has on occasion been used to control mania in pregnant patients, especially in the first 3 months. Acceptable combinations include calcium channel blockers and diuretics, beta-blockers and diuretics, dihydropyridine calcium channel blockers and beta-blockers, or dihydropyridine calcium channel blockers with either verapamil or diltiazem.

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