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Mechanisms and Drugs Influencing the Heart and Vascular System

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Abstract

The introduction of long-acting dihydropyridines such as extended-release nifedipine, amlodipine, felodipine, isradipine, nicardipine, and nisoldipine has led to fewer adverse events. These agents should be used in combination with β-blockers. Some patients may have symptomatic relief improved more with calcium channel blockers than with β-blocker therapy.

Keywords: Pain Control; Drugs; Epidemics; Therapy; Analgesics; Opioids;

Introduction

Calcium channels are functional pores in membranes through which calcium flows down an electrochemical gradient when the channels are open. Calcium channels exist in cardiac muscle, smooth muscle, and probably many other cellular membranes. These channels are also present in cellular organelle membranes such as the sarcoplasmic reticulum and mitochondria. Calcium functions as a primary generator of the cardiac action potential and an intracellular second messenger to regulate various intracellular events [1]. Calcium enters cellular membranes through voltage-dependent channels or receptor-operated channels. The voltage-dependent channels depend on a trans-membrane potential for activation. Receptor-operated channels either are linked to a voltage-dependent channel after receptor stimulation or directly allow calcium passage through cell or organelle membranes independent of trans-membrane potentials [2]. There are three types of voltage-dependent channels: the T, L, and N channels. The T and L channels are located in cardiac and smooth muscle tissue, whereas the N channels are located only in neural tissue. The T channel is activated at low voltages in cardiac tissue, plays a major role in cardiac depolarization, and is not blocked by calcium antagonists. The L channels are the classic "slow" channels, are activated at higher voltages, and are responsible for phase II of the cardiac action potential. These channels are blocked by calcium antagonists. Calcium channel blockers interact with the L-type calcium channel and are composed of drugs from four different classes: the dihydropyridine derivatives, the phenylalkyl amines, the benzothiazepines, and diarylaminopropylamine ether. The L-type calcium channel has specific receptors, which bind to each of the different chemical classes of calcium channel blockers. Systemic hemodynamic effects of calcium channel blockers represent a complex interaction among myocardial depression, vasodilation, and reflex activation of the autonomic nervous system. Nifedipine, like all dihydropyridines, is a potent arterial dilator with few veno dilating effects. Reflex activation of the sympathetic nervous system may increase HR. The intrinsic negative inotropic effect of nifedipine is offset by potent arterial dilation, which results in lowering of BP and increase in CO in patients. Dihydro-pyridines are excellent antihypertensive agents, owing to their arterial vasodilatory effects. Antianginal effects result from reduced myocardial oxygen requirements secondary to the afterload-reducing effect and to coronary vascular dilation resulting in improved myocardial oxygen delivery [3].

Discussion

Verapamil is a less potent arterial dilator than the dihydropyridines and results in less reflex sympathetic activation. In vivo, verapamil generally results in moderate vasodilation without significant change in HR, CO, or SV. Verapamil can significantly depress myocardial function in patients with pre-existing ventricular dysfunction. Diltiazem is a less potent vasodilator and has fewer negative inotropic effects compared with verapamil. Studies in patients reveal reductions in SVR and BP, with increases in CO, pulmonary artery wedge pressure, and ejection fraction [4]. Diltiazem attenuates baroreflex increases in HR secondary to NTG and decreases in HR secondary to phenylephrine. Regional blood flow to the brain and kidney increases, whereas skeletal muscle flow does not change. In contrast to verapamil, diltiazem is not as likely to aggravate congestive heart failure, although it should be used carefully in these patients. Coronary artery dilation occurs with the calcium channel blockers with increases in total CBF. Nifedipine is the most potent coronary vasodilator, especially in epicardial vessels, which are prone to coronary vasospasm. Diltiazem is effective in blocking coronary artery vasoconstriction caused by a variety of agents, including α-agonists, serotonin, prostaglandin, and acetylcholine [5]. Calcium channel blockers exert their primary electro-physiologic effects on tissue of the conducting system that is dependent on calcium for generation of the action potential, primarily at the sinoatrial and atrio-ventricular nodes. They do not alter the effective refractory period of atrial, ventricular,or His-Purkinje tissue. Diltiazem and verapamil exert these electro-physiologic effects in vivo and in vitro, whereas the electro-physiologic depression of the dihydropyridines is completely attenuated by reflex sympathetic activation. Nifedipine actually can enhance SA and AV node conduction, where-as verapamil and diltiazem slow conduction velocity and prolong refractoriness of nodal tissue. Nifedipine was the first dihydropyridine derivative to be used clinically. Other dihydropyridines available for clinical use include nicardipine, isradipine, amlodi-pine, felodipine, and nimodipine [6]. In contrast to the other calcium channel blockers, nimodipine is highly lipid soluble and penetrates the blood-brain barrier. It is indicated for vascular spasm after intracerebral bleeding. Nifedipine's oral bioavailability is approximately with peak plasma levels occurring

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within minutes. Protein binding is and elimination half-life is approximately in hours. Nifedipine is available for oral administration in capsular form. The compound degenerates in the presence of light and moisture, preventing commercially available intravenous preparations. Puncture of the capsule and sublingual administration provide an onset of effects in minutes. Nicardipine is a dihydropyridine agent with a longer half-life than nifedipine and with vascular selectivity for coronary and cerebrovascular beds [7]. Nicardipine may be the most potent overall relaxant of vascular smooth muscle among the dihydropyridines. Peak plasma levels are reached 1 hour after oral administration, with bioavailability. Plasma half-life is of hours. Although the drug undergoes extensive hepatic metabolism with less than the drug excreted renally, greater renal elimination occurs in some patients. Plasma levels may increase in patients with renal failure; reduction of the dose is recommended in these patients. Verapamil's structure is similar to that of papaverine. Verapamil exhibits significant first-pass hepatic metabolism, with a bioavailability [8]. One hepatic metabolite, norverapamil, is active and has a potency approximately that of verapamil. Peak plasma levels are reached within 30 minutes. Bioavailability markedly increases in hepatic insufficiency, mandating reduced doses. Intravenous verapamil achieves hemodynamic and dromotropic effects within minutes, peaking at few minutes and lasting up to few hours. Accumulation of the drug occurs with prolonged half-life during long-term oral administration. After oral dosing, the bioavailability of diltiazem is greater than that of verapamil. As with verapamil, hepatic clearance is flow dependent and major hepatic metabolism occurs with metabolites having 40% of the clinical activity of diltiazem. Hepatic disease may require decreased dosing, whereas renal failure does not affect dosing. Most significant adverse hemodynamic effects can be predicted from the calcium channel blockers' primary effects of vasodilation and negative inotropy, chronotropy, and dromotropy. Hypotension, heart failure, bradycardia and asystole, and AV nodal block have occurred with calcium channel blockers. These side effects are more likely to occur with combination therapy with β-blockers or digoxin, in the presence of hypokalemia [9]. Calcium antagonists provide excellent symptom control in patients with unstable angina. In the absence of β-drenergic blockade, the short-acting dihydropyridine nifedipine may increase the risk of myocardial infarction or recurrent angina. When β-adrenergic blockers cannot be used, and HR slowing is indicated, verapamil and diltiazem may offer an alternative. Systemic hypertension, long recognized as a leading cause of cardiovascular morbidity and mortality, accounts for enormous health-related expenditures. Nearly a fourth of the U.S. population has hypertensive vascular disease; however, these individuals are unaware of their condition and another are inadequately treated. On a worldwide basis, nearly billion individuals are hypertensive. Hypertension management comprises the most common reason underlying adult visits to primary care physicians, and antihypertensive drugs are the most prescribed medication class. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure defined systolic BPs exceeding Hg and diastolic BPs Hg as stage hypertension. BPs less than were defined as normal and those in between as consistent with prehypertension. Risk for cardiovascular disease appears to increase at BPs exceeding, with a doubling in risk associated increment in systemic pressure. Thus, the most recent JNC report recommends drug therapy for pre-hypertensive disease in patients with compelling indications, such as chronic renal disease or diabetes. Antihypertensive therapy generally is targeted to achieve systemic BPs; however, for high-risk patients such as those with diabetes or renal or cardiovascular disease, lower BP targets are suggested, typically less. More than distinct medications are marketed for treatment of hypertension. Often, combined therapy with two or more classes of antihypertensive medications may be needed to achieve treatment goals. Although the specific drug selected for initial therapy now has been deemed less important than in the past, recognition that specific antihypertensive drug classes alleviate end-organ damage, beyond that simply associated with reductions in systemic BP, has led to targeted selection of antihypertensive drug combinations on the basis of coexisting risk factors such as recent myocardial infarction, chronic renal insufficiency, or diabetes [10]. For purposes of characterizing treatment urgency, severe hypertension is characterized as either a hypertensive emergency with target organ injury or hypertensive urgency with severe elevations in BP not yet associated with target organ damage. Chronic elevations in BP, even when of a severe nature, do not necessarily require urgent intervention and often may be managed with oral antihypertensive therapy on an outpatient basis. In the most extreme cases of malignant hypertension, severe elevations in BP may be associated with retinal haemorrhages, papilledema, and evidence of encephalopathy, which may include headache, vomiting, seizure, and/or coma.

Conclusion

Progressive renal failure and cardiac decompensating are additional clinical features characteristic of the most severe hypertensive emergencies.

Acknowledgement

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Conflict of Interest

None

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