Nifedipine In Cardiovascular Disorders: A Review

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Cardiac cellular functions depend on the free cytosolic concentration of Calcium ions. Calcium ions influence the concentration of muscle cells in the myocardium as well as coronary and systemic vessels. The generation and conduction of electrical impulses in the heart is also influenced by intracellular concentration of Calcium ions. This concentration is largely dependent on the movement of Calcium ions from extracellular space into the cell through the surface membrane. "Calcium Channels" protein molecules that span the cell membrane, are the major routes through which the ions diffuse through the membrane. Fleckenstein(1) described the concept of calcium channel blockers in 1971: one of the most important concepts in modern cardiovascular pharmacotherapy.

Nifedipine is the most widely used calcium channel blocker in a number of cardiovascular diseases. It is mainly used for treatment of coronary spasm, classical angina pectoris, and systemic and pulmonary hypertension. The drug is under investigation for secondary prevention of myocardial infarction and peripheral vascular disease. In future, this drug may play a role in the treatment of hypertrophic cardiomyopathy in children.

Nifedipine is 4-(2'-nitrophenyl)-2, 6-dimethyl-3, 5-dicarbomethoxy 1, 4-dihydropyridine. The main actions of this drug are a peripheral vasodilator effect and a direct negative inotropic effect.

When nifedipine was selectively injected into the coronary arteries of human adult subjects, it produced a marked decrease in myocardial contractility. This decrease was measured by radiographic evaluation of radiopaque markers inserted into the heart. A fall in maximal left ventricular rate of development of pressure (dP/dt max) was noted (2). In some studies, the direct depression of myocardial contractility was more prominent in ischemic zones (3,4).

The vasodilator effect of nifedipine is most prominent in the arterial vascular bed. Nifedipine reduces systemic vascular resistance and cardiac afterload by inhibition of the calcium-dependent electromechanical coupling in smooth muscle cells of the vessels. When patients of coronary artery disease were treated with nifedipine, improvement in global and regional myocardial contractility was noticed (5). In patients with congestive cardiac failure, nifedipine reduces left ventricular filling pressure.

Nifedipine has a direct negative inotropic effect on diastolic properties of the heart. Intracoronary injection of nifedipine slowed the relaxation phase(6). Ludbrook and co-workers(7) reported that nifedipine did not significantly alter the overall diastolic properties of myocardium, although the left ventricular diastolic pressure-volume curve was displaced downward. However, improvement in diastolic function of the heart was noted in patients with congestive cardiac failure(8). This was concluded by White and associates by shortening the time to maximal filling at rest and increasing the peak filling rate at exercise(8).

By decreasing systemic vascular resistance and arterial pressure, nifedipine causes reflex sympathetic stimulation of the heart. This may increase the left ventricular outflow tract obstruction in patients with hypertrophic obstructive cardiomyopathy. The drug may be combined with beta-adrenoreceptor blocker to get beneficial results in this situation.

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A bolus injection of nifedipine in newborn lamb increased pulmonary artery pressure by 16% and pulmonary arterial resistance by 16%. The cardiac output was decreased by 7%, systemic vascular resistance by 38% and left ventricular dP/dt by 50% (9). It was concluded that nifedipine constricts the pulmonary arterioles of the new born lamb and has a negative inotropic effect. Coe and associates(9) recommended that nifedipine should not be used in the management of neonatal pulmonary hypertension, especially that due to hypoxia.

Nifedipine is effective in the treatment of all types of angina pectoris. Bertrand and coworkers confirmed by direct demonstration angiocardiographic and ergonovine testing as well as by long-term clinical studies that nifedipine is effective in the treatment and prevention of coronary artery spasm(10). This was reported in a study that the antianginal effect of nifedipine is greatest in patients with a component of coronary spasm (11). In patients with stable angina pectoris due to coronary artery disease, nifedipine reduces the frequency and extent of spontaneous anginal episodes and the frequency and extent of ST—segment depression. It prolongs exercise tolerance and reduces the magnitude of ST-segment depression at any given work load (12,13).

Nifedipine may preserve myocardial structure and function during acute ischemia. This effect may result by the following mechanisms, but no single mechanism has been established:

1. Accumulation of Calcium is inhibited in ischemic cells with damaged membranes, especially in mitochondria(14)

2. Collateral blood flow is increased towards the ischemic myocardium(15).

3. Myocardial oxygen demand is reduced by afterload reduction, by preload reduction, and possibly also by a direct myocardial oxygen sparing effect of the drug(16).

In patients with coronary artery disease, nifedipine reduced platelet aggregation and prolong the bleeding time. This may be mediated by inhibition of calcium transport across the platelet membrane. It may contribute to the antianginal and antiatherosclerotic effect of nifedipine. Transient regional cardioplegic effect of nifedipine as well as increased coronary flow and low myocardial oxygen consumption, may be of value during a temporary coronary occlusion. Hombach and associates(17) noted that in a significant number of patients, intracoronary nifedipine preserved myocardium from ischemic changes induced by coronary angioplasty. This allowed prolonged inflation periods that are important for successful transluminal angioplasty (17).

Nifedipine reduces elevated pulmonary pressure and vascular resistance in both primary and secondary pulmonary hypertension. In 8 patients with secondary pulmonary hypertension, nifedipine, given 20mg sublingually, decreased pulmonary vascular resistance and increased cardiac output(18). Two of these patients had Eisenmenger's syndrome. In another study by Olivari and coworkers(19), marked improvement was reported in 7 patients of primary pulmonary hypertension within an hour of sublingual administration of 20mg nifedipine. Pulmonary arterial systolic pressure was reduced from 91.7± 13.9 to 76.8 ±22.3 mmHg, pulmonary arterial diastolic pressure from 41.3 ± 12.4 to 31.9 ± 12.3 mmHg and mean pulmonary arterial pressure decreased from 58.1 ± 14.3 to 28.6 ± 16.3 mmHg. Pulmonary vascular resistance was reduced from 1070 ± 260 to 695 ± 266 dynes. sec. Cm^{-5}.

These effects have been clearly shown with short term administration of the drug, however nifedipine is found to be effective in long term therapy. The largest series of long term treatment of patients with primary pulmonary hypertension was reported by Rubin and associates(20). Six patients when treated with nifedipine 40-120 mg daily for upto 14 months, showed an increase in cardiac output and a decrease in pulmonary vascular resistance. This effect was sustained in 5 of the 6 patients. Other studies(21,22,23) reported the cases in whom this effect of nifedipine was sustained for at least several months. Fisher and co-workers suggested that the beneifical effect of nifedipine may not be generalised but may rather be selective for patients of active pulmonary vasospastic disease (24). The occurrence of Raynaud's phenomenon in these patients may indicate the presence of an active pulmonary

vasospastic disease.

There are some problems in the treatment of patients of pulmonary hypertension with nifedipine. These are, impairment of ventilation-perfusion ratio, a negative inotropic action which may cause myocardial suppression and may limit the effect of drug, and nifedipine does not reduce the elevated pulmonary arterial pressure despite a significant reduction in pulmonary vascular resistance in a considerable number of patients.

Nifedipine is also effective in the treatment of systemic hypertension by its selective dilating effect on resistance vassels. MacGregor and associates(25) have shown a greater reduction of blood pressure in hypertensive than in normotensive patients. In this study, the antihypertensive effect of nifedipine has been reported to correlate with the patient's pretreatment level of blood pressure and vascular resistance. Sublingual administration of nifedipine lowers the elevated blood pressure within 20 minutes. In long term clinical studies, it has been reported that nifedipine, administered orally in the form of capsules, 3 to 4 times daily, is effective in lowering both systolic and diastolic blood pressure at rest and during exercise(26, 27, 28).

Nifedipine elevates plasma renin activity for a short period only (29). It causes only minimal sodium retension despite activation of the renin-angiotension system. This effect is possibly because nifedipine decreases the aldosterone response to angiotensin II (25, 30, 31). When compared to other vasodilator drugs used in hypertension therapy, nifedipine was found to cause less sodium and water retension (29). As sodium and water retension in arterial walls contributes to the development of patient's tolerance to the vasodilator drug, tolerance to nifedipine does not usually develop in hypertensive patients, although in a few patients tolerance may develop especially when nifedipine is administered alone 32).

In summary, nifedipine is the most widely used calcium antagonist, useful for treatment of all forms of angina pectoris. The drug is also used for treating systemic and pulmonary hypertension. By preserving myocardial structure from ischemic changes it may be useful during coronary angioplasty, and it is under investigation for treatment of hypertrophic cardiomyopathy in children.

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