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# Nifedipine

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Nifedipine is a calcium channel blocking agent gaining widespread acceptance in the treatment of hypertension and angina. It acts as an arterial vasodilator in coronary and peripheral vascular beds without major effects on cardiac contraction or impulse conduction. Continuing clinical investigations have consistently demonstrated the safety and efficacy of nifedipine in these situations, making it an increasingly important drug in emergency care.

## THE ROLE OF CALCIUM IN MUSCLE CONTRACTION

A muscle cell is stimulated to contract by an electrical impulse from a nerve or an adjacent cell. The electrical stimulus sets off a chain of events, called depolarization, which moves specific ions in and out of the cell across its outer membrane.

In cardiac muscle cells, depolarization depends on the opening of special channels in the cell membrane for sodium and calcium ions (1,2). Once in the cell, calcium binds to troponin. When troponin is bound to calcium, the strands of muscle protein, actin and myosin, are free to link together. Actin and myosin strands may then slide together in an interleaving fashion (Figure 1). After depolarization and contraction, sodium and calcium are pumped back out of the cell. As calcium is pumped out, troponin is free to again wedge itself between actin and myosin, preventing linkage and contraction.

The vascular smooth muscle cell mechanisms are slightly different than those of cardiac muscle cells. Contraction of vascular smooth muscle appears to be dependent upon two different types of mechanisms (3). The first mechanism, electro-mechanical coupling, is mediated by electrically triggered calcium channels, which open in response to depolarization of the membrane. Extracellular calcium may then diffuse into the cell to initiate the contractile process. The second mechanism, pharmaco-mechanical coupling, involves a receptor site stimulation induced contraction that occurs without depolarization of the membrane. It results from the release of calcium retained in the cell, within the sarcoplasmic reticulum (3). This effect also results in an additional influx of extracellular calcium via the receptor-oriented channels on the outer cell membrane. The free intracellular calcium, brought there by either mechanism, results in binding of calcium to calmodulin. The calcium-calmodulin complex activates an enzyme, myosin light-chain kinase, that allows binding to occur between actin and myosin. These two separate but interwoven fibers, now linked, can then slide together to cause vascular smooth muscle contraction (4).

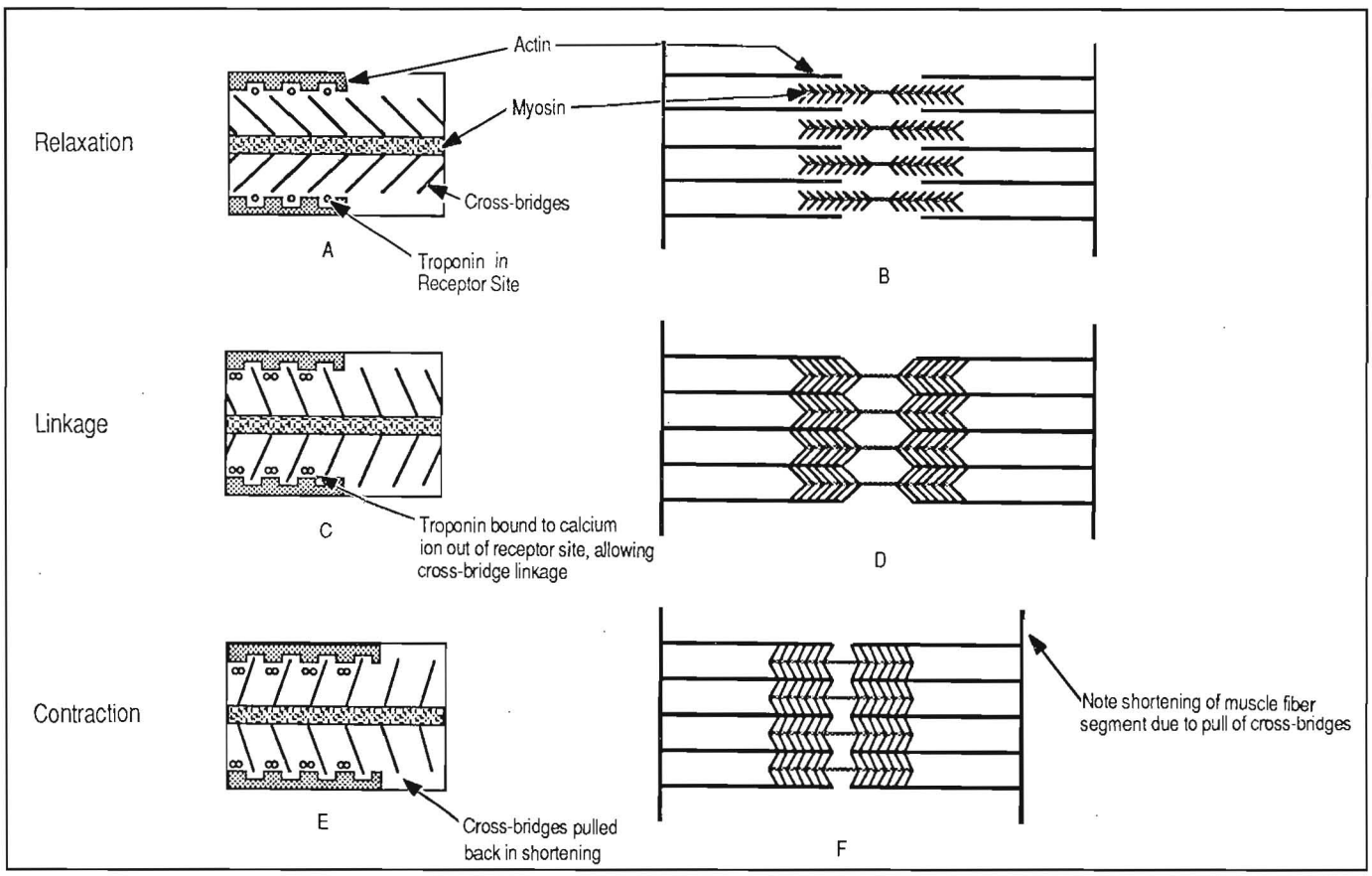
## ACTIONS

The actions of calcium channel blockers have undergone extensive study and clarification, but the molecular basis of their actions remains unclear. Evidence regarding the presence of specific receptors for calcium channel blockers is incomplete. It has been suggested by Herscheler et al. that these drugs may have to cross the cell membrane to gain access to receptor sites on the inner (cytosolic) surface of the membrane to enable them to block the calcium channels (5). It is also unclear whether these drugs block calcium channels by entering the mouth of the channel, by interacting directly with the channel proteins, or by disordering or otherwise modifying specific regions of the membrane and thus altering the functional response of the calcium channel proteins within the membrane (6). Although the exact mechanisms of action calcium channel blockers have not been described, their therapeutic actions have been extensively documented.

### Cardiac Effects

Intravenous and intracoronary administration of nifedipine has been shown to increase coronary sinus oxygen saturation and coronary artery diameter in normal and post-stenotic segments (7-9). Many studies have shown that administration of nifedipine to patients with coronary artery disease (CAD) results in increases in coronary blood flow (9-12). The greatest increases appear to occur following intracoronary administration, followed by intravenous, sublingual, and oral administration, in that order. Engel and Lichtlen showed nifedipine increased coronary blood flow to myocardial tissue served by both normal and stenotic coronaries. Relative to baseline values, percentage increases in coronary flow to myocardial tissue served by stenotic coronaries were greater than those in tissues served by normal coronaries (11).

Malagoff et al. suggested that the beneficial effects of nifedipine on coronary blood flow in patients with CAD may




M. Gunderson, H. Shuster

**Figure 1 - Calcium in muscle contraction** - Figures A (detail view) and B illustrate the relaxation phase of mucle fiber proteins. Note the presence of troponin molecules in A, blocking the receptor sites needed for cross-bridge linkage between actin and myosin. Figures C and D show establishment of cross-bridge linkage. In C, note the receptor site has formed a cross-bridge after the troponin was pulled out and bound by the calcium. Figures E and F show how cross-bridges pivot to move the actin and myosin together in an interleaving fashion. The contracted legnth of the muscle fiber is shown in figure F.

be related to a decrease in resting coronary vascular tone (13). The dilation of large epicardial coronary arteries after intracoronary administration of nifedipine is prolonged and suggests that nifedipine predominantly results in sustained relaxation of the epicardial conductance vessels, while intramural arterioles are only transiently dilated (7,10). Nifedipine has little effect on coronary sinus flow or myocardial oxygen consumption either at rest or during exertion. Thus, the overall effects of nifedipine are consistent with mild coronary vasodilatory action, reduced coronary arterial resistance and increased myocardial blood flow, usually without a significant reduction in myocardial oxygen consumption (14).

The acute administration of sublingual nifedipine has been shown to increase heart rate in cardiac patients and normal volunteers (15). The increases in heart rate have ranged between statistical insignificance to increases of up to twenty-eight percent over control values. These increases in heart rate are due to a baroreceptor mediated increase in beta-adrenergic tone secondary to systemic vasodilatation (6). Although nifedipine may induce a statistically significant increase in heart rate, it does not produce clinically significant changes in the maximum sinus node recovery time, sinoatrial conduction time, atrio-ventricular conduction time, QRS duration or the QT interval in patients with normal electrocardiac function (15). Thus, nifedipine has no direct chronotropic properties of its own.

## Cardioprotective Effects

Myocardial ischemia and subsequent reperfusion may cause accumulation of excess free intracellular calcium which can lead to inhibition of adenosine triphosphate (ATP) production by the mitochondria. In turn, a depression of ATP synthesis can eventually affect the sodium and calcium pumps to ultimately cause even more calcium accumulation in the cell and mitochondria - a vicious cycle that may destroy the ATP generating capacity of the mitochondria. Increased intracellular calcium appears to be partly responsible for ischemic myocardial cell death (16). Inhibition of the inward

transport of calcium by means of calcium channel blockers may therefore prevent mitochondrial calcium overload and consequently preserve the structure and function of myocardial cells, protecting against the deleterious effects of hypoxia and ischemia (12,17,18).

Animal studies have shown that nifedipine augments collateral flow into the ischemic myocardium after coronary occlusion and decreases infarct size while preserving ventricular function (18,19). There are conflicting data regarding the effect of nifedipine in limiting the extent of ischemic injury after acute myocardial infarction in humans (20, 21).

It is likely that other mechanisms may contribute to the cardio-protective effects of nifedipine. Other possible mechanisms may include inhibition of calcium dependent platelet aggregation (22), the effect of nifedipine on coronary hemodynamics and myocardial oxygen supply, and the ability of nifedipine to retard and/or prevent the onset of arrhythmias associated with ischemia (23).

### Peripheral Vascular Effects

Sublingual nifedipine may elicit significant increases in cardiac output and decreases in left ventricular filling pressure as a result of the reductions in systemic vascular resistance (24). These increases in cardiac output and reductions in systemic vascular resistance are due to direct arteriolar vasodilatation with reductions in impedance to left ventricular ejection (25-27). Decreases in left ventricular filling pressure may be related to an improvement in ventricular emptying due to afterload reduction (27). Reductions in pulmonary vascular resistance associated with increases in the cardiac index further suggests a selective effect of nifedipine on arterial resistance vessels (28). Afterload reduction has also been demonstrated by the consistent lowering of left ventricular, systolic and diastolic volumes (26,29).

The magnitude of the decreases in systemic vascular resistance due to nifedipine administration has been inversely correlated with initial values, indicating that basal vascular tone is very important in modulating the response to arterial vasodilatation (26,29). Greater decreases in systemic vascular resistance have also been seen in patients with abnormal than in those with normal left ventricular function (24). Nifedipine reduces left and right ventricular end-diastolic pressures in patients with impaired left ventricular function (24,26) but does not alter the filling pressures of those with normal left ventricular function (24). Nifedipine may also effect a striking improvement in left ventricular ejection fraction and ejection rate in both subjects with normal or impaired left ventricular function (26). Likewise, cardiac output has increased significantly in patients with impaired left ventricular function but remained unchanged in those with normal left ventricular function (24). Thus, the reduction of left ventricular preload by nifedipine is not due to venous pooling but rather to improved left ventricular systolic function in response to afterload reduction. This is especially true in patients with impaired left ventricular function (24).

## PHARMACOKINETICS

Close to one hundred percent of a single oral or sublingual dose of nifedipine is absorbed, although only forty-five to sixty-eight percent of the drug reaches the systemic circulation and is bioavailable (22). Considerable variations in peak plasma nifedipine concentrations have been measured after oral and sublingual administration. Time required to reach peak levels have been reported from thirty to one hundred eighty minutes (22,30). Presumably, these variations are due to differences between individuals in the rate of drug absorption and/or variability in the extent of nifedipine breakdown as it first passes through the liver.

The steady state volume of distribution of nifedipine in man after oral administration is 1.32 liters/kg and 0.62-1.12 liters/kg for intravenous administration (30). Nifedipine protein binding to albumin is concentration dependent and has ranged from 92 to 98% (22,30). Nifedipine undergoes almost complete (95%) hepatic oxidation via microsomal oxidases to three pharmacologically inactive metabolites which are excreted in the urine (22).

The elimination half-life of nifedipine is apparently dependent on the dosage form in which it is administered, with half-lives of 6-11 hours, 2-3.4 and 1.3-1.8 hours measured after oral tablet, oral capsule and intravenous administration, respectively (22). The total systemic and intrinsic clearances of nifedipine from plasma have ranged from 27 to 66 liters per hour and 33 to 37 liters per hour, respectively (22). Renal impairment does not significantly alter nifedipine pharmacokinetics.

At the present time, nifedipine is only available commercially as a sealed capsule filled with gel containing 10 mg. of the drug. The capsule may be taken orally with later absorption in the G.I. tract. Sublingual administration is more appropriate for emergency situations. To administer nifedipine sublingually, the capsule should be punctured with a 18 gauge or larger needle. The capsule may then be squeezed to deposit gel beneath the tongue. The small volume of gel makes it safe even in an unconscious patient.

## EMERGENCY USE

### Classic Stable Angina

Classic stable angina is characterized by the occurrence of sudden retrosternal chest pain which is precipitated by exercise of relatively short duration and is closely associated with severe atherosclerotic coronary artery obstruction. In the majority of patients with chronic disease, their chest pain and ST segment depression are reproducible at a given work load and this appears to be directly related to an imbalance between myocardial oxygen supply and demand (31, 32). In recent clinical investigations, patients diagnosed with chronic stable angina were administered nifedipine, 30 - 60 milligrams per day, for periods of up to six weeks. It was found that anginal

attacks, assessed by consumption of glycerol trinitrate tablets, were reduced by 50-60%. Exercise tolerance was also markedly improved by nifedipine as indicated by significant increases in the time to onset of angina, maximal exercise duration and work performance at both the onset of angina and at maximal exercise (33). Sherman and Liang found that both systolic and diastolic blood pressures were significantly reduced at the onset of angina and at maximum exercise, whereas the rate pressure product (which is indicative of myocardial oxygen consumption) was not (33). Myocardial ischemia, as reflected by ST segment depression at peak exercise, was significantly reduced by nifedipine and there was a decrease in the magnitude of ST segment depression at specific levels of rate pressure product during moderate to maximal exertion (33). This data suggests that patients with chronic stable angina, the vasodilator properties of nifedipine reduce afterload while heart rate remains relatively unchanged. The drug offers clinical benefits to such patients by decreasing myocardial oxygen demand (33). Additional evidence indicates that nifedipine may augment myocardial oxygen supply by direct coronary vasodilatation, although this appears to be of lesser importance (31, 32).

### Variant Angina

Variant (Prinzmetal's) angina is a clinical syndrome characterized by episodes of spontaneous and unprovoked ischemic cardiac pain at rest (usually at night or early morning) associated with ST segment elevation and relieved by sublingual glycerol trinitrates (34,35). Although the precise mechanisms are unknown, there is substantial evidence that coronary artery spasm (of sufficient severity to induce ischemia) plays a major pathophysiological role in the ischemia of variant angina (17). The clinical efficacy of nifedipine for treatment of variant angina has been extensively documented. Ebner and Donath, in a retrospective study of 439 patients with variant angina treated with nifedipine (10-160 milligrams per day, up to six years) indicated that an overall success rate of 87 percent was achieved (36). In a large multi-center study, nifedipine eliminated attacks of variant angina in 63 percent of the patients and greatly reduced the incidence of attacks in all but 7 percent of the remaining patients (37). Stone et al. noted that complete remission of anginal attacks or reduction in anginal frequency of more than 50 percent occurred more often in patients with variant angina than in those with stable angina (38). These results indicate that nifedipine can be expected to produce a beneficial response in most patients with a vasospastic component to their angina.

### Unstable Angina

Unstable angina is a clinical syndrome which is usually diagnosed when episodes of angina increase either in frequency, severity, or duration. Such patients frequently report decreased responsiveness to anti-anginal medications or need to use them more often (39). The increased symptomatic manifestations of myocardial ischemia, with pain occurring at rest, (day or night), are often associated with reversible ECG changes in the ST segment and or the T wave. Although the vast majority of ischemic episodes abate, this is not always the case. The disease can exacerbate with development of an acute myocardial infarction. There are growing indications that coronary vasospasm may play a major role in the onset of ischemic attacks (39). This suggests that calcium antagonists may make an important contribution to their treatment. In several studies, 74% to 89% of patients with unstable angina, refractory to conventional therapy, responded successfully when nifedipine, 30 to 240 milligrams per day, was added to their treatment during short term hospitalization (9,40,41). In the largest of these trials, nifedipine at 10 milligrams, 6 times per day, was found to produce short-term stabilization of unstable angina in greater than 80 percent of patients. After two years, nifedipine, titrated between 30 and 80 milligrams per day, maintained excellent long-term benefits in 60 percent of patients (40). Although these initial results are encouraging, further studies must be made prior to absolute statements about the relative efficacy of nifedipine in unstable angina.

### Myocardial Infarction

The differentiation between angina and myocardial infarction is a common problem, particularly in the field. Sublingual nitroglycerin is a first-line drug in the treatment of chest pain without hypotension. If there is favorable response to nitroglycerin, angina is implied. Should the relief be minimal or transient, nifedipine may be considered. Should there be a vasospastic component to the angina, the relief may be dramatic.

Patients who do not have relief of chest pain with nitroglycerin are more likely to be suffering a myocardial infarction. Nifedipine may offer some clinical benefits with its cardio-protective effects. However, the potential benefits of nifedipine are likely to be offset by enlargement of the infarction due to increased myocardial oxygen demand from reflex tachycardia associated with systemic vasodilation. If the infarction is due to intense coronary vasospasm, the response to nifedipine may be very good. Unfortunately, it is difficult to tell whether a developing infarction has a vasospastic component before nifedipine is attempted. More research is needed to address the consequences of nifedipine when vasospasm is not part of the clinical picture.

### Hypertension

Approximately 25 to 30 percent of the U.S. adult population has hypertension. Of these people, 10 percent have severe hypertension (42). The primary hemodynamic abnormality in essential hypertension is an elevation of both peripheral and renal vascular resistance (43). Hemodynamic differences among patients are related to age, race, sex, and duration of hypertension (43, 44). In established hypertension, the cardiac output decreases by as much as 25 percent and there

is a marked increase in systemic vascular resistance (43). In hypertensive crisis, there is a marked increase in systemic vascular resistance because of structural changes in the vasculature (45). Therefore, therapy should be directed at correcting this hemodynamic derangement. Hypertensive crisis if untreated, often quickly results in death, usually related to central nervous system events, cardiovascular events or renal failure (44). Some patients may tolerate very high blood pressures with few symptoms or signs, whereas others may manifest end organ damage at lower blood pressures. Thus, the definition of hypertensive crisis depends on the clinical assessment of blood pressure level and clinical and laboratory assessment of end organ damage. The absolute blood pressure in itself does not determine the seriousness of the clinical situation or the necessary expediency of treatment and monitoring within the critical care unit (44). Although treatment of hypertensive crisis is generally aimed at lowering the blood pressure, it is important not to lower the blood pressure precipitously or to a subnormal level. This is of particular importance in patients with some degree of end organ damage (42). Such treatment may critically reduce blood flow and perfusion to vital organs and exacerbate a cerebral or myocardial ischemia or renal failure (42,46). Smooth, gradual reduction of blood pressure is crucial to patient management. Thus, a return to normal blood pressure should be avoided in the first few days of therapy (44,46). The arterial blood pressure should be controlled at about 160/100 millimeters of mercury for the first few days until the body can adjust to lower blood pressure levels (44,46).

Hypertensive crisis may occur when the diastolic blood pressure is 120 to 130 millimeters of mercury in association with end organ damage that is either progressive or present at the time of the initial evaluation (42). Most patients with a hypertensive crisis should be treated expeditiously, within minutes to an hour (46,47). Administration of calcium channel blockers is an ideal approach to treatment of patients with hypertensive crisis. These drugs reduce blood pressure by decreasing the intracellular calcium available in vascular smooth muscle cells. Through vasodilatation, nifedipine reduces blood pressure in patients who have hypertension as well as high peripheral vascular resistance. However, the drug minimally affects blood pressure levels in subjects within the normal range and with normal vascular tone (48). Nifedipine's vasodilatory effect is proportional to vascular resistance prior to its administration (49). Moreover, cardiac output increases acutely after administration of nifedipine to patients with hypertension. This increase is a result of baroreflex activation which causes an increase in blood flow (49).

Many studies have shown that nifedipine can reduce blood pressure effectively with minimal side effects in patients with hypertensive crisis (46-48, 52). Bertel et al. showed that 10 to 20 milligrams of oral nifedipine markedly reduced blood pressures in a heterogeneous group of patients with severe hypertension, within 30 minutes (48). In the treatment of a group of patients with hypertensive crisis, Ellrodt et al. found that sublingual nifedipine produced a significant decrease in systolic, diastolic and mean arterial pressures within five minutes of administration. Although there were considerable variations in individual responses, 97, 90 and 67% of patients achieved diastolic blood pressures of less than 120, 110, and 100 millimeters of mercury, respectively, in the first sixty minutes (51). Haft, in treating 63 patients with diastolic pressures over 120 millimeters of mercury or systolic pressures over 200 millimeters of mercury, or both, found that all of the patients tested had blood pressures less than 200/100 in twenty to thirty minutes following 10 to 20 milligrams of nifedipine sublingually (52). He noted no side effect in any of the patients, even though 37 of them were taking at least one other anti-hypertensive medication. The reduction of blood pressure was prompt, smooth, and predictable (46-48, 50-52).

In hypertensive encephalopathy and acute cerebral vascular accidents associated with severe hypertension, the rapid reduction of blood pressure is critical in limiting tissue damage. In both of these conditions, the integrity of the microvasculature is compromised. Resultant increased capillary permeability causes interstitial edema, thereby contributing to cerebral cellular dysfunction and death. Excessive arterial pressures (exceeding cerebral autoregulation) leads to increased fluid pressure which exacerbates cerebral edema and its consequences (52,53). Similarly, inadequate cerebral blood flow leads to cellular hypoxia, capillary leak, and edema (53). A rapid fall in blood pressure in patients with severe hypertension may result in permanent ischemic brain damage because of disturbances in autoregulation of cerebral blood flow (53). Strandgaard et al. noticed a reduction in cerebral blood flow in chronically hypertensive patients with mean arterial pressures below 120 millimeters of mercury (54). Thus, an acute reduction of 30 percent from baseline is recommended to avoid underperfusion of the chronically hypertensive cerebrum (53). Bertel et al. found cerebral blood flow significantly increased after administration of nifedipine in patients with severe hypertension (48). Several other investigators have yielded similar results, showing the efficacy and safety of nifedipine in the management of severe hypertension without cerebral compromise (49-53).

The patient experiencing a hypertensive crisis may be encountered in the field. In order to minimize further end organ damage, expeditious reduction of the systolic and diastolic pressure must be achieved. Sublingual nifedipine administered in the field is very effective toward this goal. The advantage of nifedipine over other anti-hypertensives is that nifedipine will reduce blood pressure towards a point of normal vascular tone. It has little effect beyond that point (48,49). Thus, nifedipine may be administrated without the sophisticated hemodynamic monitoring that may be appropriate with other types of agents.

Systemic hypertension and ischemic heart disease frequently occur in the same patient (55). There are several reasons for this. First, hypertension is a well-known risk factor for coronary atherosclerosis. Second, several of the diseases or conditions associated with one of these two disorders are often associated with the other. For example, systemic hypertension often results in renal disease and uremia

accelerates coronary atherosclerosis. An increased incidence of both hypertension and symptomatic coronary atherosclerosis is found in patients with obesity, diabetes mellitus, or a long history of cigarette smoking. In patients with severe coronary atherosclerosis and in those with mild to moderate coronary artery disease having considerable left ventricular hypertrophy, hypertension is an important determinant of increased myocardial oxygen demand (55). Patients with a combination of hypertension and ischemic heart disease frequently have depressed left ventricular function and often develop signs and symptoms of left-sided heart failure (53,55). In numerous studies reporting the results of nifedipine in patients with hypertensive crisis and associated left ventricular failure, nifedipine markedly reduced systemic and pulmonary arterial pressures and relieved pulmonary edema (26, 53, 56). Nifedipine induced a striking reduction in left ventricular pressure (26.5 millimeters of mercury to 17 millimeters of mercury) and increased cardiac index (2.76 liters per minute to 3.77 liters per minute), as reported by Cohan and Checcio, when administered to patients in acute cardiac failure. Olivari noted that nifedipine produced no intravascular volume expansion, no alteration in glomerular filtration rate and no changes in plasma renin activity in the treatment of his patients (57). The net effect of nifedipine in hypertensive patients associated with ischemic heart disease is reduction of blood pressure, increased coronary blood flow, marked improvement in left ventricular function, and relief of pulmonary edema (26,53,55,57).

## SIDE EFFECTS

Analysis of composite studies of nifedipine usage worldwide has shown an overall incidence of side effects of about 20 percent (58). These side effects, which are generally extensions of the vasodilating effects of nifedipine, can be alleviated by either decreasing the nifedipine dose, or by combining the drug with a beta blocker (22). Side effects from nifedipine increase with larger dosage. Thus, oral tablets (slow release) are indicated for long term therapy (59). Ebner and Donath presented an analysis of side effects based on 4,863 patients (36). It was shown that side effects usually occurred within the first 14 days of chronic treatment. The most frequent side effects were headache, flushing, dizziness, gastrointestinal symptoms, and fluid retention, in that order. Cardiovascular side effects most commonly included tachycardia and hypotension (60). Tachycardia was generally transient due to the baroreceptor reflex of the acute vasodilatation. The incidence of hypotension was dose related, occurring in 5% of patients receiving greater than 120 milligrams of nifedipine a day (60). Stone et al. (38) reviewed 716 cases of patients with refractory angina and noted that 14% of the patients experienced an increase in angina frequency during chronic nifedipine treatment. He also noted that an exacerbation of acute anginal symptoms was more common in patients with classical exertional angina than in patients with either variant or unstable angina. It was reasoned that these patients had only a small vasospastic component in their ischemic heart disease. Schanzenbächer et al. described a worsening of cardiac ischemia in several high risk patients on beta blockers or nitrates when the addition of nifedipine caused hypotension (10). It was later shown that this could be prevented by an adjustment in the dosage of nifedipine (55). Several other potential side effects have been reported in a few patients but their relationship to nifedipine has not been clearly established (22). The reported frequency with which side effects, most commonly those related to vasodilatation, required discontinuation of nifedipine has been reported to be 2 to 6% (36, 60). This has led most investigators to consider nifedipine as a relatively safe agent in the treatment of ischemic heart disease and hypertension (14, 25, 28, 32-39, 46-53, 55, 56).

## DRUG INTERACTIONS

Several pharmacokinetic drug interactions have been reported for calcium entry blockers. Many of these can be ascribed to the extensive hepatic metabolism of these drugs, but their clinical relevance remains to be evaluated (61). However, when other agents metabolized by the microsomal oxidative system are used concurrently, there can be potential interactions for either drug.

Cimetidine, a widely-used agent for gastrointestinal disorders, has been shown to reduce hepatic blood flow and inhibit hepatic microsomal oxidative functions (62). When either oral or intravenous nifedipine was administered to patients taking Cimetidine, the bioavailability was nearly doubled while the clearance was decreased by about 40 percent (62). It was also noted that Cimetidine exacerbated the hypotensive effects of nifedipine (61). Ranitidine has not been shown to interact with nifedipine and should be considered for use in place of Cimetidine in patients concurrently taking nifedipine (61). Cigarette smoking has been show to stimulate both the heart rate and the activity of hepatic microsomal oxidases. These effects would be antagonistic to the action of any anti-anginal agent, because increased heart rate increases myocardial oxygen demand, while increased drug metabolism results in lower plasma levels of the drug (61).

There are conflicting clinical reports regarding the interaction of nifedipine with digoxin. Recent studies have shown nifedipine having no effect on levels of digoxin in normal or cardiac patients (63,64). Although it appears safe to use nifedipine in digitalized patients, caution should be exercised when initiating this combination.

A pharmacokinetic interaction apparently occurs between nifedipine and quinidine in some patients. Farringer et al. reported two cases in which concurrent nifedipine therapy

appeared to decrease serum quinidine levels (65). This continuation of nifedipine therapy resulted in an increase in serum quinidine concentrations from 2/2.5 to 4.6 micrograms per milliliter in one case and from 1.2 to 4.0 micrograms per milliliter in the other. Thus, this combination should be used with caution, particularly because of the rebound increases in serum quinidine levels after nifedipine is discontinued. Similarly, if adequate serum concentrations of quinidine cannot be obtained, concurrent nifedipine administration should be ruled out before larger doses of quinidine are ordered (61).

## PRECAUTIONS IN SELECTED PATIENTS

Since nifedipine is extensively metabolized by the liver, liver disease would most certainly have the potential to modify the pharmacokinetic parameters with this drug, with resultant increases in half-life. Thus, for cirrhotic patients, half the normal intravenous dose is appropriate. The oral dosage should start from 25% of the normal oral regimen.

Elderly patients experience changes in both hepatic drug oxidation and hepatic blood flow during the aging process. Therefore, dosaging should be conservative (61). Until more data regarding the use of nifedipine in the elderly is available, patients over the age of 70 years should receive low dosages of the drug initially.

Nifedipine has not been approved for use in the lactating mother or in the pediatric patient.

Nifedipine should be used with caution in patients with renal disease or diabetes mellitus until further studies establish their safety in such patients.

## COST CONSIDERATIONS

In the American medical practice, the course of therapy considered most beneficial to the patient has traditionally governed clinical management. The increasing popularity of HMO's, PPS's and other prepaid medical plans has led to an increasing pressure to constrain rising health care costs. Cost consideration of therapy has become an important aspect of patient management. In a recent study by Luce et al., the cost implications of the use of nifedipine as compared to nitroprusside in the definitive care of acute, severe hypertension was reviewed (66). The investigators found that patients who received nifedipine in the emergency department, when compared with those who received nitroprusside, showed a significant savings. These savings ranged from $270 for the first day to $1,437 for a four day period (66). The primary reason that was cited for this difference involved a less urgent need for close monitoring of patients on nifedipine who would otherwise be receiving a parenterally administered drug. The authors concluded that nifedipine was less costly than nitroprusside for the treatment of patients with hypertensive emergencies (66).

## SYNOPSIS

Nifedipine has shown to be an effective and relatively safe agent in the treatment of all grades of angina and mild to severe hypertension. Its rapid onset and smooth predictable effects make it particularly useful in the emergency setting.

Hypertensive emergencies must be controlled within an hour in order to limit end organ damage. The therapeutic choices available to the paramedic and emergency department are limited by administration and hemodynamic monitoring requirements. Until recently, diuretics and beta blockers were the only reasonable treatments available. What was needed was an agent that could lower patients blood pressure quickly, safely and predictably. It also needed to be easily administered and without the need for extensive hemodynamic monitoring. Nifedipine meets these requirements. It is easily administered by piercing a 10 milligram capsule and evacuating its contents sublingually. It is absorbed quickly and near completely with its vasodilating effects seen within five to ten minutes and peak effects seen in thirty to sixty minutes. The decrease in blood pressure is directly proportional to pretreatment vasoconstriction and peripheral resistance levels. Therefore, the reduction in blood pressure is predictable. Side effects are seen in approximately 20 percent of patients treated with nifedipine but are generally limited to dizziness, flushing, and occasional tachycardia.

The coronary vasodilating effects of nifedipine are useful with various forms of angina, especially if vasospasm is a major underlying component. This drug has been used for years for this indication and with impressive results. Besides relieving the coronary vasospasm, nifedipine dilates coronary arteries thereby increasing the supply of blood to the heart. This can lead to a reduction in ischemia and improved cardiac function in some patients.

Nifedipine should prove to be a valuable and effective tool in the management of patients with angina or hypertension in the prehospital, emergency department or other acute care settings.

## REFEREE COMMENTARY

*Robert B. Pettyjohn, D.O. (Emergency Department, Metropolitan General Hospital)* - Nifedipine has been used extensively in the Pinellas County EMS system with very good results. In our experience as a metropolitan EMS system responding to approximately 71,000 emergency calls per year, we have seen few failures or complications with nifedipine in the field. This paper points out the pharmacologic aspects of nifedipine quite well. I am not aware of any evidence that sublingual nifedipine has an advantage over sublingual nitroglycerin in treatment of classic angina. However, sublingual nitroglycerin has a much lower cost per dose than nifedipine.

*Brian Cobb, M.D. (Internal Medicine PGY-4, University of South Florida College of Medicine)* - Mr. Wilbur has provided an excellent and comprehensive review of the pharmacology and clinical

applicability of nifedipine in emergency care. Nifedipine is useful in the treatment of angina, malignant hypertension, and hypertensive urgencies. Although the drug is quite safe and effective, it bears repeating that blood pressure should be carefully monitored after administration to detect excessive lowering, which could result in worsened cerebral or myocardial ischemia. We have had good results with the drug in both angina and hypertension. Emergency physicians should, however, consider the short duration of action of the antihypertensive effect and provide an appropriate regimen for sustained control before discharging patients where hypertension has been treated with nifedipine. While prompt relief of chest pain with nitrates suggests angina rather than myocardial infarction, one should bear in mind that the pain of MI can also be relieved with nitrates.

Mr. Wilbur's Response - I agree with Dr. Pettyjohn that that there is no evidence showing that sublingual nifedipine is preferable to sublingual nitrates in treatment of classic angina. Nitrates are still the drug of choice. However, if sublingual nitrates do not relieve acute cardiac pain of unknown etiology, nifedipine should be considered as it may be very beneficial if the etiology turns out to be vasospastic with variant angina or MI secondary to vasospasm. In the normotensive patient with thrombic MI, there is no evidence showing harm from nifedipine. If the thrombic MI patient is hypertensive, nifedipine may provoke a reflex tachycardia with an increase in myocardial oxygen demand that is theoretically deleterious, but this tachycardia is transient. In either case, the nifedipine is beneficial by limiting mitochondrial damage secondary to excessive intracellular calcium influx in the ischemic myocardial tissues. I agree with Dr. Cobb's remarks. I would like to thank both Dr. Pettyjohn and Dr. Cobb for their comments.

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