

**LONG-ACTING NIFEDIPINE IN THE MANAGEMENT OF THE HYPERTENSIVE PATIENT****Dr. P. H. Prajapati, Dr. H. D. Karen and Harsh Vaghela\***

Department of Pharmaceutic, Shri Sarvajani Pharmacy College, Gujarat Technological University, Arvind Baug, Mehsana-384001, Gujarat, India.

**\*Corresponding Author: Harsh Vaghela**

Department of Pharmaceutic, Shri Sarvajani Pharmacy College, Gujarat Technological University, Arvind Baug, Mehsana-384001, Gujarat, India.

Article Received on 18/11/2018

Article Revised on 10/12/2018

Article Accepted on 31/12/2018

**ABSTRACT**

Hypertension is a global condition affecting billions worldwide. It is a significant contributor to cardiovascular events, cardiac death and kidney disease. A number of medication classes exist to aid healthcare providers and their patients in controlling hypertension. Nifedipine, a dihydropyridine calcium channel blocker, was once one of the most widely used medications for hypertension, but safety and tolerability concerns along with the introduction of new classes of antihypertensive medications and an increasing pool of data showing mortality benefit of other classes caused nifedipine to fall out of favor. More recently, long-acting formulations were developed and made available to clinicians. These newer formulations were designed to address many of the concerns raised by earlier formulations of nifedipine. Numerous clinical trials have been conducted comparing long-acting nifedipine to many of the more commonly prescribed antihypertensive medications. This review will address the pharmacology, pharmacokinetics and the available clinical trial data on long-acting nifedipine and summarize its role in the management of hypertension.

**KEYWORDS:** Nifedipine, calcium channel blockers, hypertension.**INTRODUCTION**

Hypertension is a progressive disease that affects more than 1 billion people around the world. The risk of developing hypertension increases with age and according to the Framingham Heart Study, even those who have a normal blood pressure (BP) at the age of 55 still carry a lifetime risk for developing hypertension of 90%. Over time, untreated or poorly controlled hypertension can lead to acute illness such as myocardial infarction and stroke. Long-standing hypertension is also a risk factor for chronic comorbidities ranging from coronary artery disease to kidney disease to left ventricular hypertrophy and heart failure.

**Pharmacology**

Nifedipine exerts its effect in hypertension, as well as angina, by acting as an arterial vasodilator. Calcium ions regulate smooth muscle contractions contributing to inotropic and chronotropic activity in the heart. The L-type channels in vascular smooth muscle permit the entrance of calcium ions which potentiates a contraction. Dihydropyridine CCBs such as nifedipine bind to the L-type channel in arterial tissue, particularly coronary arteries, preventing the influx of calcium ions which allows for vasodilation, thus increasing myocardial oxygen supply. Myocardial oxygen demand is reduced with the decrease in peripheral vascular resistance. CCBs

are also responsible for a decrease in afterload, illustrated by a decrease in systolic BP (SBP). The decrease in BP depends on the baseline value such that patients with a higher BP will experience a more significant reduction. Several studies have also shown a decrease in the development of new atherosclerotic lesions with the use of dihydropyridine CCBs which is attributed to their vascular protective characteristics.

**Pharmacokinetics**

Nifedipine displays zero-order kinetics across the dosing range from 30 mg to 180 mg with an estimated elimination half-life of 1.7 hours. This is significant considering the effect on heart rate (HR) and BP corresponds to plasma drug concentration. Renal impairment does not affect the half-life of nifedipine unless it is severe ( $CrCl < 25$  mL/minute), in which case the half-life is extended to approximately 3.8 hours. Sixty to eighty percent of the dose is excreted as an inactive metabolite in the urine. Nifedipine is hepatically metabolized and is 92% to 98% protein bound. Due to significant first-pass metabolism nifedipine's bioavailability is between 45%–68%. Chronic liver disease may prolong the disposition half-life and increase the bioavailability. Studies have been conducted that compare various nifedipine formulations in an attempt to establish if there is a clinically significant benefit of one

extended-release Formulation over another. It has been established that the reflex activation of the SNS correlates with the rate of increase in plasma drug levels. Thus it is hypothesized that a more gradual rise in drug concentrations should decrease SNS activation, in turn reducing adverse events associated with short acting Nifedipine. One such trial of 25 patients compared nifedipine GITS 60 mg once daily to either nifedipine prolonged action 20 mg twice daily or two 10 mg nifedipine capsules every 8 hours under fasting conditions. This trial failed to demonstrate a relationship between peaks plasma drug concentrations with the three formulations and BP reduction, which opposes the findings of previous studies the author concluded that patients should not be switched between formulations because although there was no correlation with BP, peak plasma drug concentrations may correspond to reflex activation of the SNS, thus inducing cardiovascular events.

### Clinical trials

Nifedipine has been compared head-to-head with several other antihypertensive, particularly when the GITS formulation<sup>1252</sup> Vascular Health and Risk Management 2008:4(6) Snider et al was released. With a diminished concern for reflex Inactivation nifedipine had the potential to play a larger role in the management of hypertension. In a 10-week, multi-center, double-blind study of 102 participants, patients received nifedipine GITS 30 or 60 mg daily, hydrochlorothiazide (HCTZ) 25 or 50 mg daily, or placebo. The major it of patients in the active treatment arms finished the study on 50 mg of HCTZ or 60 mg of nifedipine GITS. Both treatments were significantly better than placebo in decreasing SBP and DBP with 71% of the HCTZ group and 67% of the nifedipine group achieving a sitting DBP  $\leq$  90 mmHg. The authors concluded that nifedipine GITS monotherapy decreases BP with efficacy similar to that of HCTZ. In another double-blind study, patients received nifedipine GITS or sustained-release propranolol for 8 week, both of which could be titrated to an optimal dose if the DBP remained  $\leq$  90 mmHg. The main objective of the trial was to evaluate the change in BP from Base line as well as the proportion of patients whose BP was decreased to goal. The majority of patients in the nifedipine and propranolol groups ended the trial on 90 mg and 240 mg daily, respectively. In this study, sitting SBP was decreased a mean of 15.9 mmHg in the nifedipine group compared to 5.7 mm Hg in the propranolol group ( $p < 0.001$ ) sitting DBP was reduced by a mean of 10 mmHg in the nifedipine arm versus 6.1 mmHg in the propranolol group ( $p < 0.018$ ). Standing SBP was also reduced to a greater extent in the nifedipine group ( $p < 0.005$ ). The proportion of patients receiving nifedipine who achieved a goal decrease in sitting and standing BP was 61% and 52%, respectively, as compared to 25% and 28% in the propranolol group. This study showed nifedipine GITS to be more efficacious than sustained-release propranolol in reducing sitting SBP and DBP, as well as standing SBP.

### Chronotherapy

It has been well documented that HR and BP vary throughout the day in a circadian pattern and one hypothesis suggests the daily increases in HR and BP correspond to a recurrent rise in norepinephrine. This theory is supported by the fact that the incidence of ischemic events such as myocardial infarctions and stroke is highest in the morning. Numerous studies have evaluated the correlation between the time of day extended-release nifedipine is administered with NE levels and subsequent cardiovascular events. One double-blind, randomized, parallel-group trial of 557 patients compared controlled-onset extended-release (COER) verapamil 180 mg taken at bed time with nifedipine GITS 30 mg taken in the morning for a maximum of 10 weeks. Doses were increased in a step-wise fashion to a goal SBP  $\leq$  140 mmHg and DBP  $\leq$  90 mmHg. The mean doses of nifedipine GITS and COER-verapamil at the end of the trial were 64 mg and 314 mg, respectively. The primary efficacy endpoint was the change in BP from baseline following four weeks of a consistent treatment dose. Therapies were determined to be equal if the mean change from baseline was  $\leq$  5 mmHg for SBP and  $\leq$  3 mmHg for DBP. After 10 weeks of treatment there was no significant difference in the mean change of early morning BP between treatment arms. There was a statistically significant difference in early morning HR between the two therapies ( $p < 0.001$ ), however the clinical significance of the 4 beats/minute decrease with COER-verapamil as compared to the 2 beats per minute increase with nifedipine GITS is minimal. The rate of rise in BP and HR in the early morning may be one of the more predictive factors in relation to cardiovascular events. This trial demonstrated that both therapies decreased the rate of increase in BP compared to baseline; however nifedipine GITS increased the rate of rise in HR while COER-verapamil significantly decreased the rate of rise in HR ( $p < 0.001$ ). The early morning HR-SBP product, an index of myocardial oxygen demand, was calculated after 4 and 10 weeks of treatment and showed that COER-verapamil significantly decreased the HR-SBP product compared with nifedipine GITS at 4 and 10 weeks ( $p < 0.0001$  and  $= 0.0003$ , respectively). The greatest extent of lowering by COER-verapamil was between 4:00 AM and 8:00 PM. The largest difference occurred between 6:00 AM and 6:00 PM; the smallest difference was found between 10:00 PM and 4:00 AM. Twenty-four hour ambulatory BP values were also monitored after 4 and 10 weeks of therapy. Recordings demonstrated that 24 hour Mean awake and sleep DBP were similar between groups. This trial attempted to dose nifedipine GITS and COER-verapamil in a manner so that peak drug concentrations would be achieved at the time when BP and HR peak the most rapidly, in the early morning; however there was no significant difference in mean change in morning BP between groups.

### Tolerability

Extended-release nifedipine appears to be relatively well tolerated, particularly compared with other antihypertensive, because it does not cause depression of the central nervous system or orthostatic is. Common adverse events mentioned in the literature are summarized. The most significant adverse effect, edema, is dose related and occurs in 10% to 30% of patients who are receiving 180 mg. When compared with placebo, headache and edema were more common in the nifedipine extended-release group. When nifedipine GITS was compared with COER-verapamil the overall incidence of adverse effects was similar between groups (74% and 68%, respectively). Peripheral edema (22% vs 4%,  $p < 0.001$ ) and arthralgia's (6% vs 2%,  $p = 0.048$ ) were reported significantly more often in the nifedipine GITS group compared to the COER-verapamil group. When the GITS formulation was compared to prolonged action and capsule formulations nifedipine GITS was better tolerated with respect to overall adverse events, particularly headache and dizziness. Only vomiting was more common in the nifedipine GITS arm compared to the other formulations. Quality of life has been assessed in patients on different dihydropyridine CCBs. One such study investigated the change in quality of life from baseline assessed by the distress of side effects and symptoms of patients receiving either nifedipine GITS 30 mg or amlodipine 5 mg daily. Patients were assessed using the Higher Symptom Distress Index score where higher scores were indicative of more distress. Mean quality of life scores were comparable between groups at baseline. Lower extremity edema (24.2% vs 17.4%), flushing (8.4% vs 10.7%), and headache (12.4% vs 11.2%) were reported in 5% of patients receiving either nifedipine or amlodipine with no difference between groups. Fifteen percent of patients receiving nifedipine and 14% of patients receiving amlodipine withdrew before the study's completion due to adverse events. Patients treated with nifedipine had more distress secondary to shortness of breath, constipation, and tachycardia as opposed to the amlodipine arm which had more distress as a result of thirst and loss of taste. The Mental/Emotional Health scale improved significantly ( $p = 0.012$ ) from baseline in patients receiving nifedipine. The Psychological Distress scale ( $p = 0.021$ ), Anxiety subscale ( $p = 0.012$ ), and Depression subscale ( $p = 0.071$ ) also improved from baseline; however the Depression subscale did not improve significantly. In the amlodipine group, significant improvements were seen in the Mental/Emotional Health scale ( $p = 0.038$ ), Psychological Well-Being ( $p = 0.042$ ), and General Positive Affect subscale ( $p = 0.037$ ); however there was a significant decrease in the Sexual Symptom Distress score ( $p = 0.045$ ). In terms of the Quality of Life Summary scale, patients receiving nifedipine GITS showed a significant improvement in score ( $p < 0.05$ ) while those receiving amlodipine did not change from baseline. This trial showed that differences in quality of life scores may be attributable to the delivery system.

### CONCLUSION

Clinicians have known for decades that nifedipine is effective at lowering BP. However, its use was curtailed when newer and seemingly safer options were introduced in the form of new drug classes and additional agents within the class of dihydropyridine CCBs. In the years that followed, several classes of antihypertensive were shown to provide a significant reduction in morbidity and mortality in high risk patients; this propelled these classes of drugs to the forefront of hypertension management, specifically ACEIs, ARBs, and  $\beta$ -blockers. Thiazide diuretics have also proven their utility in managing hypertension patients and are widely accepted as a first-line option in patients devoid of a compelling reason to be prescribed another class of antihypertensive. Based on the clinical trial data described above, it appears that many of the concerns surrounding the older formulations of Nifedipine have been addressed with the GITS formulation. Edema still appears to be relatively common, although timing of dosing may ameliorate this effect. While data are not yet available for long-term mortality benefit of long-acting nifedipine, it is reasonable to consider this medication in situations where other dihydropyridine CCBs would commonly be used (eg, as add-on therapy to improve the patient's likelihood of achieving their BP goal or as initial therapy in patients that need general coronary artery disease prevention and do not have a compelling reason for prescription of another class of antihypertensive). Aggressive use of long-acting nifedipine as a first-line antihypertensive is not supported by clinical data or current practice guidelines. A number of clinical trials evaluating long-acting nifedipine have recently been completed or are ongoing. These include trials evaluating the effects of nifedipine on NE, delivery of nifedipine via osmotically controlled-release oral delivery system (OROS) combination therapy with telmisartan, the effects of nifedipine on proteinuria and BP in patients with diabetes, the effect on renal function decline and efficacy compared with Lisinopril. The results of these may provide additional insight into the most appropriate use of long-acting nifedipine.

**Disclosures:** The authors do not have any conflicts of interest related to the content of this publication.

### REFERENCES

1. Blood Pressure Lowering Treatment Trialists' Collaboration. Effects of different blood-pressure-lowering regimens on major cardiovascular Events: results of prospectively-designed overviews of randomized trials. *Lancet*, 2003; 362: 1527–35.
2. Brown MJ, Palmer CR, Castaigne A, et al. Morbidity and mortality in patients randomized to double-blind treatment with a long-acting calcium-channel blocker or diuretic in the international nifedipine GITS study: intervention as a goal in hypertension treatment (INSIGHT). *Lancet*, 2000; 356: 366–72.

3. Champlain J, Karas M, Nguyen P, et al. Different effects of nifedipine and amlodipine on circulating catecholamine levels in essential hypertensive patients. *J Hypertens*, 1998; 16: 1357–69.
4. Chung M, Reitberg DP, Gaffney M, Singleton W. Clinical pharmacokinetics of nifedipine gastrointestinal therapeutic system: a controlled release formulation of nifedipine. *Am J Med*, 1987; 83(suppl 6B): 10–4.
5. Chobanian AV, Bakris GL, Black HR, et al. The seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: The JNC 7 Report. *JAMA*, 2003; 289: 2560–72.
6. Dahlof B, Devereux RB, Kjeldsen SE, et al. Cardiovascular morbidity and mortality in the Losartan Intervention for Endpoint reduction in hypertension study (LIFE): a randomized trial against atenolol. *Lancet*, 2002; 359: 995–1003.
7. Fogari R, Mugellini A, Zoppi A, et al. Differential effects of lercanidipine and nifedipine GITS on plasma norepinephrine in chronic treatment of hypertension. *Am J Hypertens*, 2003; 16: 596–9.
8. Fogari R, Preti P, Zoppi A, et al. Effect of telmisartan/hydrochlorothiazide combination versus nifedipine GITS on ambulatory blood pressure and sympathetic activation. *Am J Hypertens*, 2005; 18: 577–83.
9. Frishman WH, Garofalo JL, Rothschild A, et al. Multicenter comparison of the nifedipine gastrointestinal therapeutic system and long-acting propranolol in patients with mild to moderate systemic hypertension receiving diuretics. *Am J Med*, 1987; 83(suppl 6B): 15–9.
10. Frishman WH, Garofalo JL, Rothschild A, et al. The nifedipine gastrointestinal therapeutic system in the treatment of hypertension. *Am J Cardiol*, 1989; 64: 65F–9F.
11. Gavras I, Mulinari R, Gavras H, et al. Antihypertensive effectiveness of the nifedipine gastrointestinal therapeutic system. *Am J Med*, 1987; 83(suppl 6B): 20–3.
12. Gibbons RJ, Abrams J, Chatterjee K, et al. ACC/AHA 2002 guideline update for the management of patients with chronic stable angina: summary article: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines (Committee on the Management of Patients with Chronic Stable Angina). *J Am Coll Cardiol*, 2003; 41: 159–68.
13. Hermida RC, Ayala DE, Mojón A, et al. Chronotherapy with nifedipine GITS in hypertensive patients: improved efficacy and safety with bedtime dosing. *Am J Hypertens*, 2008; 21: 948–54.
14. Hermida RC, Calvo C, Ayala DE, et al. Dose- and administration time-dependent effects of nifedipine GITS on ambulatory blood pressure in hypertensive subjects. *Chronobiol Int*, 2007; 24(3): 471–93.
15. Izzo JL, Jr, Levy D, Black HR. Clinical Advisory Statement: importance of systolic blood pressure in older Americans. *Hypertension*, 2000; 35: 1021–4.