

Clinical Outcome of a Mandatory Formulary Switch for Dihydropyridine Calcium Channel Blocker Therapy at a Veteran's Administration Medical Center

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Abstract

Recently, changes in antihypertensive therapies with similar properties have been made based primarily on cost savings for hospital formularies. To assess blood pressure (BP) control and adverse side effects associated with a switch of patients on nifedipine GITS to felodipine at our Veteran's Administration Medical Center (VAMC), we prospectively studied physician records and patient-reported side effects (both from the medical record and patient questionnaires) in 127 hypertensive patients (70 ± 10 years, 95% men, 88% nonblack, 44% with coronary disease) who underwent the forced switch in therapy. During the period of patient visits/chart review, physicians were unaware that the study was being conducted. A minimum of 2 months and two visits on each therapy was required for patient inclusion. The mean doses of nifedipine GITS and felodipine used were 55 ± 24 mg/day and 8 ± 2.6 mg/day, respectively. The use of supplemental antihypertensive agents was similar in both calcium channel blocker groups. Systolic BPs and heart rates were similar in patients taking the two drugs, and the diastolic BP was modestly lower in patients taking felodipine (78 ± 10 mm Hg for felodipine and 80 ± 10 mm Hg for nifedipine, $P < 0.05$). There were no differences in the incidence of side effects (both patient-reported and provider-reported) for the two antihypertensive therapies. These data demonstrate that in an hypertensive population followed in a VAMC, mandatory switching of stable dihydropyridine calcium channel blocker therapy did not result in any significant changes

in short-term (2 to 3 months) BP control nor were adverse side effects different based on both physician- and patient-reported sources of information.

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In recent years, formulary changes in antihypertensive therapies with similar properties have been made based primarily on cost savings for institutional pharmacies.¹ Using cost alone could be short-sighted as several issues are of relevance to patients and their physicians when using antihypertensive agents, including efficacy, tolerance and acceptability, convenience of use, need for additional or supplemental therapy, and compliance.¹⁻⁴

In early 1994, the pharmacy manager at our Veteran's Administration Medical Center (VAMC) made a decision to replace nifedipine gastrointestinal therapeutic system (GITS) with felodipine extended-release tablets as the dihydropyridine calcium channel blocker in the formulary. This decision was based on a substantial savings in acquisition costs to the institution. At the time of this decision, there were no direct comparisons between the two drugs. However, efficacy and side effect rates appeared to be similar from previous clinical trials.^{5,6} Subsequently, one comparative clinical trial of these two agents by Fagan et al⁷ did show similar blood pressure changes among gender and race subgroups as well as similar incidences of side effects.

Generally, the impact of policy changes in therapy in clinics with "closed" formularies are not assessed formally by clinicians. Thus, we took the opportunity to evaluate the effects of this switch from nifedipine GITS to felodipine in an observational study of a cohort of hypertensive veterans using outcome measures of office blood pressures and heart rates, supplemental antihypertensive drug use, and adverse side effects.

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... METHODS ...

Patient Population

Patients taking nifedipine GITS were identified using the computerized pharmacy data base. Of 540 patients taking nifedipine, there were 251 patients who were scheduled to undergo the change in therapy during the study period of March 1, 1994 to September 1, 1994. Patients were included in the study if they had a history of hypertension and had been on a stable dose of nifedipine GITS for at least 3 months immediately before the switch in therapy. In addition, patients were required to have follow-up care in our outpatient department and have at least two clinic visits during felodipine therapy with the first visit a minimum of 1 week or greater after the change in therapy and a second visit no less than 2 months after the change in therapy. Patients were not included in the evaluation if they were lost to follow-up, switched to another antihypertensive therapy within 2 months of the initial switch, or failed to have at least two clinic visits by the time of the study termination. Patients were also excluded if they were taking nifedipine for indications other than hypertension (eg, Raynaud's disease or vasospastic angina without hypertension).

Before the formulary switch, providers were briefly informed by the pharmacy of the institutional decision to change the dihydropyridine calcium channel blocker available at the institution, given the cost considerations. The only other information supplied to the practitioners were a predefined dosing conversion scale sent to them by the pharmacy. The dosing conversion scale recommended that patients on a total daily dose of 30 to 60 mg of nifedipine once daily should be switched to 5 mg of felodipine once daily and those individuals taking nifedipine, 90 mg once daily, should receive a starting dose of felodipine at 10 mg once daily. There were no patients in the pharmacy records who were taking a dose of 120 mg of nifedipine daily. In general, the patient population served by the institution receives all of their medications at the VAMC pharmacy.

All patients attended the VAMC outpatient clinics and were cared for by supervised internal medicine residents or physician extenders (physicians' assistants/nurse practitioners), and attending internists. The providers and patients were unaware of the conduct of the study. This study was approved by the institutional Review Board of the University of Connecticut Health Center. In addition, patient questionnaires were sent to subjects as part of a formal VAMC drug utilization and evaluation process.

Data Collection

Two research assistants (ST and CD) evaluated the computerized pharmacy records at the end of each week to identify patients who had been switched to felodipine. Through the computerized scheduling office, it was then possible to determine the date of the next scheduled outpatient visit. Medical records were reviewed to identify patients who met the study criteria and then abstracted as appropriate. Patient demographics, weight, blood pressure, heart rates, and physical examination data, comorbidity, use of supplemental antihypertensive medications, as well as side effects/adverse experiences while on nifedipine and felodipine were obtained. The values for the measurements of weight, blood pressure, and heart rate from the two visits while on nifedipine and the values for the two visits after the switch to felodipine were averaged. Side effects and supplemental drug use were obtained from all recorded visits.

A clinical questionnaire on aspects of patient satisfaction and side effects was developed by the research staff (WBW, ST) and mailed to the 251 patients involved in the formulary switch after they had been on felodipine for several weeks. Specific questions regarding side effects common to the dihydropyridine calcium channel blockers (eg, edema, headache, flushing) were posed as well as general health questions. In addition, we asked patients to comment on the level of satisfaction with the change in antihypertensive therapy. The questionnaires were mailed in preaddressed and prestamped envelopes back to the office of the VAMC associate chief of service for ambulatory care.

Analysis

To evaluate quality control of the chart abstraction, a sample of 40 records was reviewed by another investigator. The level of agreement in levels of blood pressure, frequency of side effects, and use of supplemental antihypertensive agents were assessed.

Changes in weight, blood pressure, and heart rate were analyzed by analysis of variance. The categorical variables (proportion of side effects and supplemental drug use) were analyzed using a χ^2 test or McNemar test.

... RESULTS ...

Study Population

Of the initial cohort of 251 patients who were switched to felodipine, 127 patients met all of the study criteria. Two patients were excluded because they had been on nifedipine for an indication other than hypertension and one patient was lost to follow-

up. The other subjects (n = 121) not included in the analysis either lacked a second visit during felodipine therapy at the closeout of the data collection period, had not been taking nifedipine for at least 3 months before the mandatory switch, or were no longer taking felodipine at the end of the observation period.

Table 1 shows the characteristics of the 127 patients before the switch. The population was generally older men with a high proportion of comorbid illnesses, including 44% with a history of coronary artery disease. The mean dose of nifedipine was 54 ± 24 mg/day and felodipine was 8 ± 2.6 mg/day. The compliance rate of attending scheduled appointments at the clinics was 96%. Body weight was unchanged after the switch to felodipine therapy.

Blood Pressures and Heart Rates

Clinic blood pressure and heart rate data are shown in Table 2. There was no difference in the group's systolic blood pressure on the two agents; however, the diastolic blood pressure was slightly, but significantly lower in patients taking felodipine compared to patients taking nifedipine (-2 ± 2 mm Hg, *P* < 0.05). A subanalysis of clinic blood pressure and heart rates grouped according to the calcium channel blockers used as a monotherapy versus use in combination with

Table 1. Demographic and Clinical Characteristics of Patients (n = 127)

| | |
|----------------------------------|---------|
| Age (years) | 70 ± 10 |
| Gender (males, %) | 95 |
| Ethnicity | |
| White (%) | 86 |
| Black (%) | 12 |
| Other (%) | 2 |
| Weight (kg) | 88 ± 16 |
| Comorbidity | |
| Presently smoking (%) | 20 |
| History of coronary disease (%)* | 44 |
| History of heart failure (%) | 9 |
| Diabetes mellitus (%) | 31 |
| Renal insufficiency (%)† | 7 |
| Hyperlipidemia (%) | 28 |
| Peripheral vascular disease (%) | 18 |

*Angina pectoris, antiischemic therapy, history of myocardial infarction, or history of coronary revascularization.

†Serum creatinine ≥1.8 mg/dL.

one or more antihypertensive agents, showed no differences in blood pressure or heart rate values for nifedipine versus felodipine (Table 2). Supplemental

Table 2. Provider Blood Pressure and Heart Rates on Nifedipine Versus Felodipine

| Parameter | Nifedipine | Felodipine |
|---|------------|------------|
| All patients (n) | 127 | 127 |
| Systolic BP (mm Hg) | 147 ± 18 | 146 ± 17 |
| Diastolic BP (mm Hg) | 80 ± 10 | 78 ± 10* |
| Heart rate (beats/min) | 74 ± 10 | 74 ± 11 |
| Monotherapy patients (n) | 36 | 37 |
| Systolic BP (mm Hg) | 149 ± 15 | 149 ± 17 |
| Diastolic BP (mm Hg) | 79 ± 9 | 79 ± 9 |
| Heart rate (beats/min) | 77 ± 8 | 78 ± 9 |
| Patients on one additional agent (n) | 49 | 49 |
| Systolic BP (mm Hg) | 147 ± 16 | 147 ± 16 |
| Diastolic BP (mm Hg) | 81 ± 9 | 78 ± 11 |
| Heart rate (beats/min) | 75 ± 11 | 74 ± 10 |
| Patients on two additional agents (n) | 31 | 33 |
| Systolic BP (mm Hg) | 144 ± 20 | 142 ± 16 |
| Diastolic BP (mm Hg) | 79 ± 11 | 76 ± 9 |
| Heart rate (beats/min) | 70 ± 7 | 72 ± 8 |
| Patients on three or more additional agents (n) | 10 | 9 |
| Systolic BP (mm Hg) | 146 ± 26 | 142 ± 22 |
| Diastolic BP (mm Hg) | 75 ± 12 | 75 ± 12 |
| Heart rate (beats/min) | 64 ± 7 | 71 ± 16 |

**P* = 0.02.

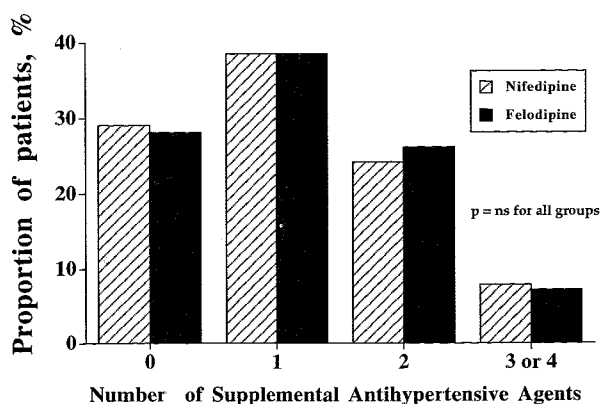


Figure 1. Number of patients on calcium channel blocker monotherapy versus one, two, or three supplemental antihypertensive drugs.

drug use was nearly identical while on nifedipine versus felodipine therapy (Figure 1).

Quality Control

Independent chart abstraction by an investigator (GG) of an unselected subsample of 40 subjects demonstrated similar findings to the research assistants, including the effects of nifedipine and felodipine on blood pressure and heart rate (blood pressure during nifedipine, 143/81 ± 14/7 mm Hg and during felodipine,

145/78 ± 16/8 mm Hg, *P* = NS; heart rate during nifedipine, 74 ± 10 beats/min and during felodipine, 74 ± 15 beats/min).

Adverse Experiences

The provider- and patient-reported adverse experiences are shown in Table 3. Approximately half of the patients returned the questionnaire (130 of 251 or 52%). The most commonly reported adverse experiences for both drugs by either source was edema of the lower extremities. However, patients reported edema approximately twice as frequently as the medical providers (Table 3). Other commonly reported side effects by the patients included fatigue, dizziness, and headaches. There were no differences in the patient-reported adverse experiences for nifedipine versus felodipine. Commonly recorded adverse experiences by providers were angina pectoris, fatigue, claudication, and dizziness. Again, the incidence of these adverse events was similar for the two calcium channel blockers.

Patient satisfaction with the formulary switch was qualitatively high, with few negative comments on questionnaires. In addition, a high percentage (87%) of patients remained on felodipine therapy as of February 1995 (approximately 1 year after the formulary switch was mandated). The reasons for discontinuation in 16 patients included lack of efficacy, intervening surgery, and adverse side effects either alone or in combination.

... DISCUSSION ...

In this observational study, we took the opportunity to evaluate the clinical outcome in a cohort of hypertensive patients who underwent a mandatory change in dihydropyridine calcium channel blocker therapy at a VAMC with a pharmacy restricted to use by local patients. We found that after the switch from nifedipine GITS to felodipine extended-release tablets, patients had similar control of blood pressure, side effect profiles, and supplemental antihypertensive drug use during a follow-up period of approximately 3 months. Thus, it is probable that the drug acquisition cost savings, which served as the primary impetus for the formulary switch, was a cost-effective maneuver for the VAMC.^{4,8}

As this study took place in an older, highly compliant population of veterans,

Table 3. Adverse Experiences Reported by Patients and Providers

| Adverse Effect | Nifedipine n (%) | Felodipine n (%) |
|---------------------------------|---------------------|---------------------|
| From patient reports (n = 130) | | |
| Leg swelling | 40 (31) | 36 (28) |
| Headaches | 3 (2) | 4 (3) |
| Fatigue | 2 (2) | 5 (4) |
| Dizziness | 4 (3) | 6 (5) |
| Numbness | 1 (1) | 0 (0) |
| Chest pain | 1 (1) | 1 (1) |
| All other | 8 (6) | 10 (8) |
| From provider reports (n = 127) | | |
| Edema, lower extremities | 21 (17) | 14 (11) |
| Angina pectoris | 14 (11) | 7 (6) |
| Fatigue | 5 (4) | 5 (4) |
| Claudication | 5 (4) | 5 (4) |
| Dizziness/lightheadedness | 4 (3) | 7 (6) |
| All other | 14 (11) | 7 (6) |

with a high rate of follow-up, it was possible to perform this observational evaluation in a relatively short period of time. It is likely that blood pressure and heart rate data after 2 or more months on an antihypertensive therapy is representative of the drug's long-term efficacy.^{9,10} To assure some consistency for the evaluation of blood pressure control, given the observational nature of the study, we used values of blood pressure and heart rate obtained at two visits after the switch to felodipine to compare to the two visits immediately before the switch while the patient was treated with nifedipine. In addition, the patients were required to have been treated for at least 2 to 3 months on each agent to qualify for the study. Finally, a subgroup analysis of the blood pressure control based on the number of antihypertensive drugs (a surrogate marker for disease severity) revealed no significant difference among the groups with regard to the blood pressure control (Table 2).

In a study by Hilleman et al,⁸ comprehensive costs of calcium channel blocker therapy were evaluated in a 7-year retrospective cost-minimization analysis of 232 hypertensive patients. In this study, felodipine was noted to have slightly lower acquisition costs than nifedipine GITS and similar costs for laboratory studies, patient visits, and side effects. Blood pressure control was not directly evaluated. Cumulative annual costs of felodipine were slightly greater than nifedipine GITS because of much higher supplemental drug usage. In contrast, in our VAMC population, supplemental drug use was nearly identical for the two calcium channel blockers (Figure 1). Thus, in our patient population, if other costs items (efficacy, side effects, clinical visits, laboratory costs) are held relatively constant, annual costs to the institution for felodipine remain reduced (about \$166 per patient) compared to nifedipine GITS based on acquisition costs alone.

There are some limitations to this observational study. The initiation of the study occurred at the beginning of the switch period and therefore used some data retrospectively from the medical records for nifedipine GITS. Although every attempt was made to avoid reporting bias (eg, blinding of the providers to the conduct of the study, verification of the chart abstraction procedure, use of similar periods and conditions of treatment, and dual sources of adverse experience data), some variables still cannot be controlled, such as reporting of adverse experiences by patients on multiple therapies. However, unlike a controlled clinical trial, we are observing actual physician practices and decision making. On the basis of this analysis, blood pressure control, supplemental

drug use, and adverse experiences were quite similar for the two drugs. In addition, this study was carried out in a VA cohort and was primarily male; thus, the results of this study may not be representative of the outcome in a female hypertensive population.

This observational practice study demonstrated that felodipine is at least as effective as nifedipine for blood pressure control in a cohort of older veterans with substantial comorbidity (diabetes mellitus, coronary artery disease, and peripheral vascular disease). Furthermore, as adverse experiences and supplemental drug use were similar on the two agents, it is likely that large acquisition cost savings would be associated with substantial cumulative annual cost savings as well.

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