Retrospective Analysis of Formulary Transition at Large Metropolitan HMO: Nifedipine GITS to Felodipine ER

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OBJECTIVE:

Evaluate the efficacy, safety, and cost-effectiveness of a formulary transition from nifedipine GITS (Procardia XL, Pfizer) to felodipine ER (Plendil, Astra Merck).

DESIGN:

Retrospective analysis of patient records for three months before and three months after formulary transition was initiated.

SETTING:

A mixed-model metropolitan health-maintenance organization with 110,000 members.

PATIENTS:

Health records of 246 patients with stable hypertension were reviewed.

INTERVENTION:

The formulary long-acting calcium-channel blocker was switched from nifedipine GITS to felodipine ER.

MAIN OUTCOME MEASURES:

Patient blood pressures, frequency of adverse drug events, and cost of medications.

RESULT:

Average preconversion and postconversion blood pressure values were 144/85 mm Hg and 142/84 mm Hg, respectively. Of 380 subjects, 28% were identified as hypertensive (systolic blood pressure $\geq$ 140 mm Hg and diastolic blood pressure $\geq$ 90 mm Hg) before conversion, while 21% were identified as hypertensive after the formulary switch. Differences between treatments were not statistically significant. Chest pain—the most commonly noted adverse effect during nifedipine GITS therapy (7.7%)—decreased after conversion to felodipine ER (4.1%). The most common adverse effect associated with felodipine ER was edema (8.9%). Felodipine ER

costs represented approximately 85% of nifedipine GITS costs, resulting in a 15% savings to the health care system.

CONCLUSION:

The therapeutic equivalence and comparable safety profile of the two medications combined with the 15% cost savings realized with felodipine ER validated the successful formulary switch from nifedipine GITS to felodipine ER at this health-maintenance organization.

KEY WORDS:

Formularies, Therapeutic substitution, Calcium-channel blockers, Costs, Adverse drug events, Drug efficacy, Nifedipine, Felodipine.

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When similar drug therapies exhibit comparable safety and efficacy, decisions made by health care providers as to which drug to include in their formularies may depend on factors such as cost, patient response and tolerance, drug safety with concomitant disorders, and patient and physician preference.¹ In 1992, Humana Health Care Plans, a mixed-model HMO with approximately 110,000 members, changed its formulary long-acting dihydropyridine calcium-channel blocker from nifedipine GITS (Procardia XL, Pfizer) to felodipine ER (Plendil, Astra Merck). Felodipine and nifedipine are both members of the dihydropyridine class of calcium-channel blockers, with demonstrated safe-

ty and efficacy for the treatment of essential hypertension.²⁻⁴

Although members of the dihydropyridine class have different pharmacodynamic effects, three comparative clinical trials conducted with hypertensive patients have shown these two agents to have similar efficacy and adverse event profiles.^{1,3,5} Felodipine is more selective for vascular smooth muscle over myocardial tissue than nifedipine¹; at doses producing equivalent vasodilation, felodipine lacks nifedipine's negative inotropic effect.⁷⁻⁹ The probability of similar patient health outcomes combined with a potential cost savings instigated this large metropolitan HMO to undertake this formulary switch. Humana Health Care Plans' for-

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mulary transition from nifedipine GITS to felodipine ER was initiated in September 1992 and has continued to the present.

This study, a retrospective record review of 380 patients with stable hypertension who switched from nifedipine GITS to felodipine ER between January 1993 and December 1994, was conducted to determine whether health outcomes were affected by the formulary switch. This managed care organization (MCO) also sought to determine whether felodipine ER was less expensive than nifedipine GITS, and a more cost-effective treatment of essential hypertension.

METHODS

The Humana Health Care Plans formulary was modified to convert patients on nifedipine GITS to felodipine ER in September 1992. To facilitate the formulary change, information was provided to all prescribers in the Humana system, and product interchange occurred upon renewal of prescriptions at all pharmacy sites in the Humana system. Patients without angina receiving nifedipine GITS to treat hypertension were switched to felodipine ER at a dose ratio of 1 mg felodipine ER per 6 mg nifedipine GITS.

Data Collection

Records of 380 patients who were switched to felodipine between January 1993 and December 1994 were examined. A six-month period of each record was evaluated (three months before and three months after the transition from nifedipine GITS to felodipine ER) for historical, efficacy/response, and safety data. *Historical data* included patient characteristics (age, gender, weight, height, and race) and patient history (use of other antihypertensive drugs, use of potentially interacting drugs, and duration of therapy). Records with the following variances were excluded from consideration:

- ▲ Patients diagnosed with chronic stable, unstable, or rest angina (for whom felodipine was not indicated)
- ▲ Patients who did not receive a 6:1 nifedipine GITS/felodipine ER dosage substitution in the transition period
- ▲ Pregnant patients (felodipine is not approved for use in this population)

Efficacy/response data included preconversion and post-conversion systolic and diastolic blood pressures, calcium-channel blocker doses, dosage adjustments, number of office visits, changes in therapy, treatment failures (i.e., lack of blood pressure control or discontinuation of felodipine ER treatment for medical reasons), and any new diagnoses during the three months following the change in therapy.

Safety data included all reported adverse effects.

The relative effectiveness of nifedipine GITS and felodipine ER was determined by comparing steady-state preconversion and postconversion blood pressure readings. Steady state was defined as the blood pressure reading on the conversion date for the preconversion measure and the last blood pressure value recorded during the study period for the postconversion measure. The interval between these measurements

Table 1. Patient Demographic Characteristics and Concomitant Drug Use

Characteristic	Value
Mean ($\pm$ S.D.) age (years)	59.4 $\pm$ 14.0
Age range (years)	29.5–90.1
Mean ($\pm$ S.D.) weight (pounds)	191.6 $\pm$ 51.5
Weight range (pounds)	95–395
Mean ($\pm$ S.D.) height (inches)	66.3 $\pm$ 4.2
Height range (inches)	52–77
Gender	
No. men (%)	107 (43.5)
No. women (%)	139 (56.5)
Ethnicity	
No. Caucasian (%)	131 (53.3)
No. African-American (%)	91 (37.0)
No. Asian (%)	3 (1.2)
No. Hispanic (%)	2 (0.8)
No. not indicated (%)	19 (7.7)
Adjunct Medications	
No. of patients on ACE inhibitors (%)	83 (33.7)
No. of patients on diuretics (%)	83 (33.7)
No. of patients on beta blockers (%)	38 (15.4)
No. of patients on calcium-channel blockers (%)	24 (9.8)
No. of patients on alpha blockers (%)	5 (2.0)
Interacting Medications	
No. of patients on cimetidine (%)	12 (4.9)
No. of patients on yohimbine (%)	1 (0)
No. of patients on phenytoin (%)	1 (0)
No. of patients on loxapine (%)	1 (0)
No. of patients on carbamazepine (%)	1 (0)

varied from one to three months, depending upon scheduling of visits. Hypertension was defined as a systolic blood pressure reading of ≥ 140 mm Hg and/or a diastolic reading of ≥ 90 mm Hg, consistent with the recommendation of the Fifth Report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure.¹⁰

Compliance and costs were also monitored. Compliance was based on patient prescription refills. Patients were considered to be compliant if their prescription refill included sufficient doses to cover the number of days in each patient's preconversion and postconversion period. Costs to the system were estimated based upon costs per unit dose and the frequency with which the medication was administered.

Statistical Analysis

Data were coded and entered in standard format on a VAX-11 mainframe computer at the University of Missouri at Kansas City. The database was validated using standard procedures, and an error rate of less than 1% was determined. A random selection of every fifth record was verified manually.

The effects of nominal data (gender, race, and use of other antihypertensive drugs) on the outcome of the formulary transition were assessed using chi-square analysis. Interval and ra-

Table 2. Drug Effectiveness: Blood Pressures and Hypertension Prevalence before and after Formulary Transition ($n = 246$)

Stable preconversion blood pressures	
Mean ($\pm$ SD) systolic value (range, mm Hg)	144.3 $\pm$ 20.2 (102–200)
Mean ($\pm$ SD) diastolic (range, mm Hg)	84.0 $\pm$ 13.5 (50–140)
Stable postconversion blood pressures	
Mean ($\pm$ SD) systolic value (range, mm Hg)	141.9 $\pm$ 21.1 (90–210)
Mean ($\pm$ SD) diastolic (range, mm Hg)	83.5 $\pm$ 12.0 (56–125)
Prevalence of hypertension preconversion	
No. patients with systole > 140 and diastole > 90 mm Hg (%)	68 (27.6)
No. patients with diastole > 90 mm Hg (%)	69 (28.0)
Prevalence of hypertension postconversion	
No. patients with systole > 140 and diastole > 90 mm Hg (%)	52 (21.1)
No. patients with diastole > 90 mm Hg (%)	69 (28.0)

tio data were examined using analysis of variance (ANOVA) and multiple regression procedures. Multiple regression was used to identify the potential impact of factors or clusters of characteristics on clinical outcomes and adverse drug events during the transition process. The accumulated data on safety were analyzed as net data, since it is possible that some adverse effects may be ascribed to other medications initiated following the discontinuance of nifedipine GITS.

Conclusions based upon these analyses employed traditional levels of significance ($p < 0.05$). The study was powered on the variable of blood pressure and the analysis indicated the ability to detect very small effects (0.2 for difference analyses and $r = 0.19$ for correlational analyses), with 90–95% confidence intervals.

RESULTS

Of 380 patients converted from nifedipine to felodipine during the course of the study, 246 efficacy-evaluable patient records remained after removal of excluded patients or incomplete files. The majority of patients were Caucasian (53.3%), while 37.0% were African-American. Average patient age was 59 years, and average weight and height were 87.3 kg (192 pounds) and 167.6 cm (66 inches), respectively (Table 1).

Of the 246 patients, 175 (71%) received at least one adjunct medication for hypertension during the study period, with the most frequently prescribed medications being lisinopril (27.6%) and hydrochlorothiazide (17.9%). Approximately one third of these patients also concurrently used either an angiotensin-converting enzyme (ACE) inhibitor or diuretic (or, in some cases, both) at some point during the assessment period. Approximately 10% of patients received concurrent therapy with other calcium-channel blockers. A total of 16 patients (6%) received medications that would potentially interact with calcium-channel blockers, the most common being cimetidine ($n = 12$).

Statistical analyses, including ANOVA, chi-square analy-

sis, and multiple regression, yielded no statistically significant correlations or differences in preconversion and postconversion measures. Thus, no statistically significant differences were found for any safety or efficacy parameter measured.

Record review indicated 98.5% of patients were compliant with their medication regimens. Mean preconversion blood pressure values were 144/85 mm Hg, while mean postconversion values were 142/84 mm Hg. Some 28% of subjects were identified as hypertensive (systolic blood pressure ≥ 140 mm Hg and diastolic blood pressure ≥ 90 mm Hg) during nifedipine GITS treatment, while 21% were identified as hypertensive using this definition during felodipine ER therapy. The differences in these values were not statistically significant. Mean blood pressure values and hypertension prevalence before and after the formulary transition are shown in Table 2.

Adverse effects were identified from patient-reported complaints in the medical record. Chest pain was the most common preconversion adverse effect (7.7%); prevalence decreased after the formulary conversion (4.1%). The most common adverse effect after conversion was edema (8.9%). Complete data regarding adverse effects before and after transition are in Table 3. A total of 14 new diagnoses, representing a range of medical conditions and distributed across nine patients, were recorded after transition to felodipine ER (Table 4). Only two of these (vertigo and supraventricular tachycardia) were considered to be potentially related to the new regimen.

During the study period, 27 patients (11%) stopped taking felodipine ER. Some 11 patients had no reason for the discontinuation listed in the medical record. The remainder cited these reasons for drug discontinuation: headache ($n = 4$), dizziness ($n = 2$), fixed drug eruption ($n = 2$), suspected congestive heart failure ($n = 2$), peripheral edema ($n = 2$), drug discontinued upon hospitalization ($n = 1$), "too expensive" ($n = 1$), hives ($n = 1$), and tachycardia ($n = 1$).

A one-time administrative "switching cost" was estimated to be approximately 2–4% of the medication cost. The mean dosage of nifedipine GITS across subjects was 50.0 mg/day, while the mean dosage of felodipine ER was 8.6 mg/day; both doses were within their recommended dosage ranges. The mean cost of nifedipine GITS was \$1.26/day, or \$37.77/month. The mean cost of felodipine ER was \$1.04/day, or \$31.14/month. Felodipine ER charges represented approximately 85% of nifedipine GITS charges, resulting in a 15% savings to the health care system.

DISCUSSION

A recent prospective study, involving a similar formulary switch at a VA hospital showed felodipine ER treatment to be therapeutically equivalent to nifedipine GITS therapy in a group of 87 elderly patients, most of whom were Caucasian men.¹ Likewise, this retrospective analysis of a formulary transition affecting members of a large metropolitan HMO demonstrated no significant changes in blood pressures or increases

Table 3. Prevalence of Adverse Effects before and after Formulary Transition

Adverse Effect	Preconversion		Postconversion		χ^2
	N	%	N	%	
Chest pain	19	7.7	12	4.9	2.531
Edema	13	5.3	22	8.9	2.492
Dizziness	10	4.1	12	4.9	0.190
Headache	8	3.1	15	6.1	2.234
Gastrointestinal reactions	5	2.0	7	2.8	0.342
Heart rate changes	5	2.0	7	2.8	0.342
Nocturia	3	1.2	3	1.2	0 ^a
Shortness of breath	3	1.2	4	1.6	0 ^a
Rashes	2	0.8	5	2.0	0.580
Asthenia	2	0.8	1	0.4	0 ^a
Other ^b	0	0	5	2.0	0 ^a
Flushing	1	0.4	1	0.4	0 ^a
Rhinitis	1	0.4	2	0.8	0 ^a
Sleep disturbances	1	0.4	3	1.2	0.252
Fatigue	1	0.4	3	1.2	0.252
Impotence	1	0.4	1	0.4	0 ^a

^a Where cell frequencies were 5 or less, Fisher's Exact Test was used.

^b "Other" included appetite disturbances, housemaids knee (patellar osteochondritis), and shortness of breath.

in adverse effects when nifedipine GITS was replaced with felodipine ER. The 246 patients in this analysis are typical of patients receiving treatment for hypertension. African-American individuals are disproportionately represented in both this research sample (37%) and the population of patients suffering from hypertension. The height and weight data suggest that our group was more overweight than the population in general, which is also typical of the hypertensive population. The gender distribution is fairly balanced for a cross section of hypertensive patients in this age group, since the male-to-female ratio was 44:56 (107 men; 139 women).

Data on before and after blood pressure values and frequencies with which hypertension continues to be a primary diagnosis suggest that felodipine ER is at least as effective in controlling blood pressure as nifedipine GITS. Indeed, of the 28% of all patients identified as hypertensive preconversion, approximately one fourth of these patients experienced better blood pressure control with felodipine ER.

One of the primary justifications for choosing felodipine ER as a formulary alternative to nifedipine GITS was its strong safety profile. For the large, heterogeneous patient population of a metropolitan HMO, medications with the least probability of exacerbating concomitant conditions are preferred. Clinical trials have established the safety of felodipine in patients with hypercholesterolemia, diabetes mellitus, arthritis, impaired renal function, asthma, and chronic obstructive pulmonary disorders.¹¹⁻¹⁷ Moreover, its lack of a negative inotropic effect on my-

Table 4. Additional Diagnoses First Detected in the Three Months after Transition to Felodipine ER

Diagnosis	No. Patients
Glucose intolerance	2
Degenerative changes/knee	2
Seborrhea of scalp	1
Sternal osteomyelitis	1
Possible deep-vein thrombosis	1
Myocardial infarction	1
Adenocarcinoma	1
Vertigo	1
Noninsulin-dependent diabetes mellitus	1
Supraventricular tachycardia	1
Chronic obstructive pulmonary disorder	1
Left ventricular hypertrophy	1

ocardial tissue¹⁸ may make felodipine ER a better choice than nifedipine GITS for patients with impaired cardiac function.

As seen in previous clinical trials,^{1,19} the most common adverse effects likely to be associated with felodipine in this trial were edema and headache. Overall, adverse effect data from this trial confirm that the formulary transition introduced no additional safety risks to patients. The frequency of adverse effects potentially related to medication use were similar after formulary transition to those reported before the formulary transition, as confirmed by chi-square analysis (Table 3). No statistically significant differences were found between before and after values.

Finally, the data indicate that the formulary transition provided cost-minimization support for the formulary decision. The cost to the system, per patient per month, for this class of medication was reduced by approximately 15% as a result of the conversion to felodipine ER. Although an administrative "switching cost" was estimated to be 2-4% of medication cost, as a one-time expense, it was offset by the prospect of substantial long-term savings. Thus, this one formulary change, with no additional safety risks or reduction in effectiveness of treatment, resulted in a medication cost savings of more than \$150,000 per year to Humana Health Care Plans of Kansas City.

CONCLUSION

The therapeutic equivalence and comparable safety profile of the two medications combined with a 15% cost savings realized with felodipine ER validated the successful switch from nifedipine GITS to felodipine ER at this health-maintenance organization. ■

References

1. Fagan TC, Haggert BE, Liss C. Efficacy and tolerability of extended release felodipine and extended release nifedipine in patients with mild-to-moderate essential hypertension. *Clin Ther* 1994; 16: 634-46.
2. Morgan TO. A review of the antihypertensive effects of felodipine alone or in combination. *J Cardiovasc Pharmacol* 1990; 13(suppl 4): S76-S84.
3. Sahiel E, Elirodt AG, Monk JP, Langley MS. Felodipine. A review of its pharmacodynamic and pharmacokinetic properties and therapeutic use in hypertension. *Drugs* 1988; 36: 387-428.
4. Sorkin EM, Clissold SP, Brogden RN. Nifedipine: a review of its pharmacodynamic and pharmacokinetic properties and therapeutic efficacy in ischaemic heart disease, hypertension and related cardiovascular disorders. *Drugs* 1985; 30: 182-274.
5. Gustin G, Taylor S, Daragjati C, White WB. Outcome of a formulary policy switch for dihydropyridine calcium-channel blocker therapy at a VA medical center [abstract]. *Am J Hypertens* 1995; 8(4): 78A.
6. Hosie J, Dawson A, Langin JJ, Scott M, Vernon JP. Tolerability of felodipine and nifedipine in equipotent antihypertensive doses [abstract]. Proceedings of the Pharmacological Society (Clinical Pharmacology Section), Dublin, Ireland, July 8-10, 1992. *Br J Clin Pharmacol* 1992; 34(5): 454P.
7. Kooler J, Piek J, van Wezel H, David G, Visser CA. Relative effects of intracoronary nifedipine and felodipine on myocardial contractility and oxygen consumption [abstract]. *Circulation* 1991; 84(suppl 2): II-683.
8. Todd PA, Faulds D. Felodipine. A review of the pharmacology and therapeutic use of the extended release formulation in cardiovascular disorders. *Drugs* 1992; 44: 251-77.
9. Cheng C-P, Noda T, Little WC. Comparison of inotropic effect of felodipine, nifedipine, and amlodipine in conscious dogs [abstract]. *Circulation* 1991; 84(suppl 2): II-401.
10. The Fifth Report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure (JNC V). *Arch Intern Med* 1993; 153: 154-83.
11. Nielsen MR, Winkel OP, Ahlström F et al. Effects on plasma lipids during long term antihypertensive treatment with felodipine. *Drug Invest* 1992; 4: 361-4.
12. Nilsson-Ehle P. Felodipine does not affect plasma lipid concentrations. *J Cardiovasc Pharmacol* 1990; 15(suppl 4): S112.
13. Morgan T, Anderson A. Interaction of indomethacin with felodipine and enalapril. *J Hypertens* 1993; 11(suppl 5): S338-S339.
14. Schersten BFE. Unchanged glucose homeostasis in hypertensive patients with type II diabetes mellitus during one year of treatment with felodipine and nifedipine compared with placebo [abstract]. *Am J Hypertens* 1994; 7(4) part 2: 73A.
15. Sajkov D, McEvoy RD, Cowie RJ et al. Felodipine improves pulmonary hemodynamics in chronic obstructive pulmonary disease. *Chest* 1993; 103: 1354-61.
16. Bratel T, Hedenstierna G, Nyquist O et al. Long-term treatment with a new calcium antagonist, felodipine, in chronic obstructive lung disease. *Eur J Respir Dis* 1986; 68: 351-61.
17. Patel KR, Peers E. Felodipine, a new calcium antagonist, modifies exercise-induced asthma. *Am Rev Respir Dis* 1988; 138: 54-6.
18. Plendil (felodipine) package insert. Wilmington, DE: Astra Merck, Inc. 1995 Jul.

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