Formulation of long-acting nifedipine tablets influences the heart rate and sympathetic nervous system response in hypertensive patients

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Pharmacokinetic and pharmacodynamics studies are usually carried out separately with theoretical linking or interpretations.
- The pharmacokinetics of short- vs. long-acting formulations of nifedipine is well known, but the pharmacokinetics of different once-a-day formulations of nifedipine is generally not well known by the practising physician.

WHAT THIS STUDY ADDS

- This study provides practical patient-based information linking pharmacokinetics to pharmacodynamics in one of the target populations of patients, those with hypertension, who might receive the two different drugs.

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AIMS

The haemodynamic responses to nifedipine vary between short- and long-acting formulations. However, the latter have not been compared despite marked differences in their constitution. Our 1-month randomized, crossover study was designed to compare the 30-mg osmotic, constant-release nifedipine gastrointestinal therapeutic system (N-GITS) with an encapsulated mini-tablet Coracten XL.

METHODS

Forty-four hypertensive patients aged 63 ± 7 years were studied. The formulation was changed on day 15 and (for a single dose) day 30. At days 0, 14, 15, 29 and 30, patients were monitored for 6 h after dosing, during which blood pressure (BP), heart rate (HR) and plasma levels of norepinephrine (NE) and nifedipine were measured. The primary outcome was the difference in plasma NE between formulations at the time of peak nifedipine level.

RESULTS

Systolic BP decreased rapidly after the first dose of Coracten, achieving nadir at 5 h. HR rose by 1.2 ± 8.8 beats min^{-1} . After N-GITS HR fell by 2.4 ± 7.7 beats min^{-1} ($P = 0.159$). Plasma NE was higher in the Coracten- (480 ± 38.3 pg mL^{-1}) than N-GITS-treated patients (343 ± 75.0 pg mL^{-1}) at the time of peak nifedipine concentrations (4 and 5 h, respectively) and their change from baseline was significantly ($P = 0.0046$) different. A similar difference between the drugs was seen again at days 15 and 30, at 5 h after switching formulations.

CONCLUSIONS

This study suggests that two different formulations of once-daily nifedipine result in different BP and plasma NE responses, and that switching between formulations causes opposite effects upon the sympathetic nervous response to falling BP.

Introduction

Nifedipine as the prototype calcium channel blocker of the dihydropyridine class is available worldwide in a number of different formulations administered usually once daily, but older multiple-dose daily formulations also exist. The modified release formulations have been developed to improve patient compliance by reducing dose frequency, and to improve efficacy by minimizing peak to trough fluctuations of plasma nifedipine concentration and the sympathetic adrenergic activation which these fluctuations cause. In order to delay release, a variety of formulations have been developed: erosive tablet technology (Coral) [1], encapsulation of several mini tablets (Nifedicon) [2], a hydrophilic matrix (Nifedipine ER) [3], an erosive polymer matrix (Slofedipine) [4], an eroding matrix (Sandoz retard) [5] and the gastrointestinal therapeutic system (GITS) [6]. Except for the GITS tablet, the degree of modified release is affected by food intake.

The absorption rate of nifedipine is related to its formulation [7–9]. This is important because the haemodynamic response to nifedipine is influenced by the rate of increase of its plasma concentration [10, 11]. This affects both the rate of initial fall in blood pressure (BP), and the degree of response from the sympathetic nervous system to this fall. Sympathetic compensation could both blunt the degree of sustained fall in BP and have deleterious effects on the heart and vasculature. However, no study has directly compared the relationship between the pharmacokinetics and pharmacodynamics of different once-daily formulations of nifedipine on heart rate (HR) and the sympathetic nervous system in a hypertensive population. The present study was conducted to examine this relationship.

Methods

Study design

This study was an open label, randomized, crossover design. A total of 45 subjects, mean age 63 ± 7.2 years (range

18–75 years), with newly or previously diagnosed mild to moderate essential hypertension were enrolled. Previously diagnosed subjects were included provided their BP was controlled for a minimum of 1 month on therapy with a sitting diastolic blood pressure (DBP) <90 mmHg and/or systolic blood pressure (SBP) <140 mmHg. Patients were excluded from the study if they had a medical history of cardiac disease, congestive heart failure, arrhythmia, ongoing or recent stroke or transient ischaemic attacks, Type 1 diabetes, severe liver, gastrointestinal tract or renal disease, were female who were pregnant, nursing or of child-bearing potential, and those with any known contraindication to nifedipine or other dihydropyridine calcium antagonists. The study was approved by the Ethical Committee of Addenbrookes Hospital and Cambridge University, and all patients gave informed written consent.

Subjects eligible to enter the study underwent a wash-out of antihypertensive medications, except diuretic or angiotensin receptor blockers, for a minimum of 5 days to a maximum of 1 week. At the conclusion of the wash-out period, subjects with a sitting DBP >90 to <114 mmHg and/or SBP >130 to <160 mmHg entered the study. Blood pressure was monitored daily during the wash-out period and those subjects with sitting DBP ≥ 95 to ≤ 114 mmHg and/or SBP ≥ 140 to ≤ 170 mmHg were entered into the treatment period immediately, and those experiencing a rapid rise in DBP ≥ 15 mmHg or reaching a DBP of 114 mmHg or a SBP >170 mmHg were excluded. Subjects were randomized to one of two treatment sequences and assessed under fed conditions (Figure 1). Twenty-one subjects were randomized to Sequence 1 and received nifedipine GITS (30 mg day⁻¹) for a period of 2 weeks, followed by 2 weeks of Coracten XL (30 mg day⁻¹) and then nifedipine GITS (30 mg day⁻¹) on the final day. Sequence 2 consisted of 2 weeks of Coracten XL (30 mg day⁻¹), followed by 2 weeks of nifedipine GITS (30 mg day⁻¹) and back to Coracten XL (30 mg day⁻¹) on the final day.

During the treatment period subjects were instructed to take the medication once a day in the morning with a

Figure 1

Flow chart indicates treatment assignment and crossover scheme. Each arrow represents a study day with blood samples taken for plasma nifedipine concentration, plasma catecholamines and ambulatory blood pressure (BP) and heart rate (HR) measurements. Sequence 1 is represented across the top with subjects receiving nifedipine gastrointestinal therapeutic system (N-GITS), then Coracten XL for 2 weeks, followed by a single dose of Nifedipine GITS. Sequence 2 is shown across the bottom and consists of Coracten XL, Nifedipine GITS and a final dose of Coracten XL.

glass of water. Subjects visited the clinic in the morning before their first dose (Visit 1) and 22–24 h after their previous dose on subsequent visits (Visits 2–5). At each visit patients were admitted to the clinic, an IV established and an AND blood pressure monitor (A&D Company Limited, Tokyo, Japan) connected. Study medications were administered approximately 1 h later with a standardized high-fat breakfast, excluding grapefruit. Blood samples were collected throughout the following 6 h for the measurement of plasma nifedipine and catecholamine concentrations. BP and HR measurements were recorded over 8 h.

Analytical procedures

Blood was collected in two heparinized tubes, shielded from the light, and immediately placed on ice. Plasma catecholamines were measured by high-performance liquid chromatography using electrochemical detection. [12] Nifedipine was measured by enzyme-linked immunosorbent assay [1].

Pharmacokinetic and statistical analyses

Plasma nifedipine concentration time profile including $C_{\max}$ and $t_{\max}$, under fed conditions for single dose, was determined at day 1, after 2 weeks of treatment, after switching from multidose Nifedipine GITS to Coracten XL and after switching from multidose Coracten XL to Nifedipine GITS. The $C_{\max}$ and $t_{\max}$ reported in this study were calculated over the 6 h of time that subjects were in the research unit.

The primary objective of the study was to compare the effects of the first dose of nifedipine GITS (30 mg) and Coracten XL (30 mg) on plasma norepinephrine concentrations, when measured at the time of peak nifedipine concentration. The secondary study objectives were to compare the plasma nifedipine trough to peak concentration-related effect on SBP, DBP and HR under fed conditions after multidosing (Visits 2 and 4) and after the switch from multidosing to the first dose of the alternative formulation (Visits 3 and 5). The Wilcoxon rank sum test was used to evaluate the statistical difference between plasma catecholamines, BP and HR of the two treatments. Peak-to-trough changes in these variables were also compared between treatments – after the first crossover dose, and at steady-state – by analysis of variance incorporating drug, sequence and patient as factors. All statistical analyses were conducted using a two-sided $\alpha = 0.05$ level of significance. The sample size calculation was based on a standard deviation of 83 pg ml^{-1} for plasma norepinephrine concentration. Considering the type I error rate as defined as 0.05, and a power of 90% at the clinically meaningful difference in treatment means of 100 pg ml^{-1} , it was determined that the required number of evaluable subjects was 20 per treatment arm.

Results

The demographic characteristics were similar between patients in each treatment sequence, as reported in Table 1. Of the 43 subjects randomized to one of two treatment sequences, one subject failed to complete all three treatment periods and was included in the safety analysis only. All 43 subjects had pill compliance of >90% over the 29-day study period.

Plasma nifedipine concentrations achieved after the first dose of medication, under fed conditions, are presented in Figure 2A. The initial administration of Coracten XL (30 mg) produced a rapid rise in the plasma concentrations of nifedipine, achieving a peak concentration ($C_{\max}$) of $57.2 \pm 7.61 \text{ ng ml}^{-1}$ at $3.9 \pm 1.2 \text{ h}$ (Table 2). A lag time followed Nifedipine GITS administration and a rise in plasma nifedipine concentrations was not seen until approximately 3 h post dose, increasing gradually to a maximum of $16.9 \pm 1.57 \text{ ng ml}^{-1}$ at $5.1 \pm 0.2 \text{ h}$. Patients treated with Coracten XL had higher plasma nifedipine concentrations at every time point compared with those receiving Nifedipine GITS. The greatest individual patient plasma concentration of nifedipine after the first dose was achieved in the Coracten XL group (140.1 ng ml^{-1}) compared with the Nifedipine GITS group (31.7 ng ml^{-1}) (data not shown).

SBP was reduced by both agents after first dose exposure (Figure 2B). Coracten XL treatment caused significant decreases from trough to peak nifedipine concentrations in the mean SBP ($-23.4 \pm 2.8 \text{ mmHg}$) compared with Nifedipine GITS ($-13.7 \pm 2.4 \text{ mmHg}$, $P = 0.012$, Table 2). There were no significant treatment differences seen in the reduction of DBP (data not shown). HR was lower in Nifedipine GITS-treated subjects, compared with those receiving Coracten XL, at all time points (Figure 2C). The mean HR was reduced by $2.4 \text{ beats min}^{-1}$ from trough to peak plasma nifedipine concentrations in the Nifedipine GITS-treated subjects, conversely mean HR in subjects receiving Coracten XL rose by $1.2 \text{ beats min}^{-1}$ (Table 2, $P = 0.159$).

The first dose of Coracten XL elicited a rise in plasma norepinephrine concentrations, whereas no changes in

Table 1

Summary of demographic data and baseline characteristics of the valid for safety analysis population

	Sequence 1 (n = 21)	Sequence 2 (n = 22)	Total (n = 43)
Male, n (%)	14 (67%)	13 (59%)	27 (63%)
Female	7 (33%)	9 (41%)	16 (37%)
Systolic blood pressure (mmHg)	150 ± 11	152 ± 8	151 ± 10
Diastolic blood pressure (mmHg)	93 ± 6	94 ± 6	94 ± 6
Heart rate (beats min^{-1})	67 ± 14	70 ± 12	69 ± 13
Age (years)	63 ± 7	64 ± 8	63 ± 7

Sequence 1 received Nifedipine GITS–Coracten XL–Nifedipine GITS, sequence 2 received Coracten XL–Nifedipine GITS–Coracten XL. Data are mean $\pm$ SD.

Figure 2

Mean plasma nifedipine concentrations (A), changes in systolic blood pressure (B), heart rate (C) and plasma norepinephrine concentrations (D) after the initial dose of nifedipine gastrointestinal therapeutic system (GITS) (◆) or Coracten XL (□). * $P = 0.0046$ for trough to peak change in norepinephrine between groups

Table 2

Time to peak plasma nifedipine concentrations (C_{max}) and trough to peak changes in plasma norepinephrine concentrations, heart rate and blood pressure values measured after the first dose of either Coracten XL or Nifedipine GITS at Visit 1

	Coracten XL <i>n</i> = 22	Nifedipine GITS <i>n</i> = 21	<i>P</i> -value
Visit 1			
Plasma nifedipine			
t_{max} (h)	3.9 ± 0.3	5.1 ± 0.2	
C_{max} (ng ml ⁻¹)	57.2 ± 7.61	16.9 ± 1.57	
Heart rate (beats min⁻¹)	1.2 ± 1.9	-2.4 ± 1.7	0.159
Systolic blood pressure (mmHg)	-23.4 ± 2.8	-13.7 ± 2.4	0.012
Plasma norepinephrine (pg ml⁻¹)	141.0 ± 34.2	-8.7 ± 35.5	0.005

Data are mean ± standard error.

the norepinephrine concentrations were seen after Nifedipine GITS administration (Figure 2D). The mean change in norepinephrine, from trough to peak plasma nifedipine concentrations between treatment arms was significantly greater in Coracten XL-treated subjects compared with those receiving Nifedipine GITS (Table 2, $P = 0.005$). There were no significant changes in plasma epinephrine concentrations throughout the study (data not shown).

Data collected after 2 weeks of continuous treatment (Visits 2 and 4) were combined (Figure 3). After multiple doses there continued to be a greater rise in plasma nife-

dipine concentrations after Coracten XL treatment compared with Nifedipine GITS (Figure 3A). There were no significant differences in the reduction in SBP (Figure 3B), changes in HR (Figure 3C) or plasma norepinephrine concentrations (Figure 3D) between treatments. However, it is noteworthy that the highest plasma concentration of norepinephrine (1313 pg ml⁻¹) was observed in a patient in the Coracten XL group after 2 weeks on treatment at the time of peak nifedipine plasma concentration.

Immediately after switching treatments, subjects were evaluated and the results of Visit 3 and Visit 5 combined (Figure 4). The change in plasma nifedipine concentrations was similar to that seen after the first dose in Visit 1, with consistently higher plasma nifedipine concentrations in the Coracten XL-treated subjects compared with Nifedipine GITS. This was accompanied by decreases in SBP in Coracten XL subjects compared with those treated with Nifedipine GITS (Figure 4B). There were no significant changes in HR between treatment arms (Figure 4C). Plasma norepinephrine concentrations diverged between the two treatments from 2 h post dose onward and were consistently lower in Nifedipine GITS-treated subjects (Figure 4D). Immediately after switching subjects from Nifedipine GITS to Coracten XL, the mean trough to peak change in norepinephrine concentration was significantly greater than in subjects switched from Coracten XL to Nifedipine GITS. The mean difference in trough to peak concentrations of norepinephrine was 54.5 ± 25.9 pg ml⁻¹

Figure 3

Mean plasma nifedipine (A), changes in systolic blood pressure (B), heart rate (C) and plasma norepinephrine concentrations (D) after multiple doses of nifedipine gastrointestinal therapeutic system (GITS) (◆) or Coracten XL (□). Data from Visits 2 and 4 combined

Figure 4

Effect of switching to nifedipine gastrointestinal therapeutic system (GITS) (◆) or Coracten XL (□) on plasma nifedipine concentrations (A), systolic blood pressure (B), heart rate (C) and plasma norepinephrine levels. * $P = 0.0420$ for change in norepinephrine following the switch of drugs

Table 3

ANOVA of differences in blood pressure, heart rate and plasma norepinephrine between nifedipine formulations

	Differences at crossover (Visits 3 and 5)	P-value
SBP (mmHg)	4.61 (0.47, 8.76)	0.03
DBP (mmHg)	1.02 (-2.40, 4.43)	0.56
HR (beats min ⁻¹)	1.11 (-1.22, 3.45)	0.36
Norepinephrine	-54.5 (-105.2, -3.74)	0.04
	Differences at steady-state (Visits 2 and 4)	P-value
SBP (mmHg)	5.41 (0.16, 10.67)	0.05
DBP (mmHg)	1.89 (-1.38, 5.17)	0.26
HR (beats min ⁻¹)	-0.93 (-3.22, 1.36)	0.43
Norepinephrine	-38.83 (-85.41, 7.76)	0.11

Peak to trough changes in each parameter were compared between Nifedipine GITS and Coracten XL by analysis of variance incorporating drug, sequence and patient as factors. Values are mean differences (95% CI), when results for Coracten XL were subtracted from results for Nifedipine GITS.

greater in the individuals switched to Coracten XL compared with those switched to Nifedipine GITS ($P = 0.04$) (Table 3). This treatment difference was not seen in subjects receiving multiple daily doses (Visits 2 and 4) of the same drug ($P = 0.11$).

Discussion

Nifedipine exists in a number of modified release formulations employing a variety of technologies to deliver drug to the patient. Of the many once-a-day formulations, only the GITS tablet is based on osmotic push-pull technology. The tablet consists of a two-layer core of nifedipine and osmotic polymer surrounded by a semipermeable membrane. The membrane contains a small laser-drilled hole. When swallowed, the tablet absorbs water from the gut through the semipermeable membrane. The nifedipine-containing core layer forms a suspension, which is then pushed out of the laser-drilled hole at a constant rate by the expansion of the polymer core layer. The GITS formulation delivers drug at a constant rate for approximately 16–18 h with minimal peak-to-trough fluctuation of drug, thus allowing once-daily dosing [13].

With once-a-day dosing of nifedipine the compliance of hypertensive patients has improved [14]. However, the bioavailability of nifedipine from different dosage formulations of nifedipine, except the GITS formulation, varies considerably and shows significant interactions with food [1–5]. Although it is quite common to compare drugs between drug classes, it is relatively uncommon to compare within a class and even more unusual within the same chemical entity. Moreover, with so many different once-daily formulations of nifedipine available to the prescribing practitioner it becomes important to provide some guidance on whether these formulations can be freely interchanged in managing a patient's hypertension.

In order to determine if this pharmacokinetic difference would translate into a pharmacodynamic difference, two once-daily formulations, nifedipine GITS and Coracten XL, were evaluated systematically. A 30-mg dosage strength was chosen as this represents a dose that is frequently prescribed to the hypertensive patient as either monotherapy or add-on therapy and it is a strength that is on the rising slope of the dose-response curve.

Nifedipine in the GITS formulation at 60 mg was originally shown by Chung *et al.* to exhibit a t_{max} at approximately 6 h in the fasting state [13]. In the present study considering the time interval monitored, the peak concentration of nifedipine after a meal was shown to occur at approximately 5 h for nifedipine GITS and 4 h for Coracten XL. This time for the Coracten XL formulation is generally in agreement with a previous study [1], which showed a t_{max} for plasma nifedipine after a 60-mg dose of 5 h. In the study by Schug *et al.* [1] on Coracten XL it was shown that the interindividual plasma concentration of nifedipine showed minimal variability under fasting conditions, but marked variability after food [1]. Accordingly, the C_{max} and AUC_{0-24} were significantly increased after food. By contrast, for the Nifedipine GITS formulation there was minimal variability in plasma nifedipine concentration between subjects both before and after a meal. Both the C_{max} and AUC_{0-24} were also not significantly altered by food. In the present study the plasma nifedipine concentration in hypertensive patients was greater from 3 to 6 h after dosing relative to Nifedipine GITS after the first dose. As previously shown by Kleinbloesem *et al.* and Donnelly *et al.*, the haemodynamic and reflex (sympathetic nervous system activation) response was significantly more marked in the Coracten XL-treated patients [10, 11]. However, after more chronic treatment (2 weeks) this haemodynamic and reflex response is blunted. Notably, after the patients were established on the Nifedipine GITS formulation and then switched to the Coracten XL formulation a similar pattern of response was noted to that of first exposure to Coracten XL. The implications of this are that when patients are switched between once-a-day nifedipine formulations untoward sympathetically mediated effects could occur. Reports from South Africa substantiate this possibility, in that patients switched from dihydropyridines with stable plasma concentration time profiles to Vascard (same formulation as Coracten XL) exhibited manifestations of the activation of the sympathetic nervous system such as acute coronary and cerebrovascular events [15].

Considering the relationship between the plasma concentration of nifedipine and haemodynamic response, it therefore becomes relevant to the primary care practitioner and the patient undergoing treatment to understand not only the BP effect of the drug, e.g. at the end of the dosing interval, but also at the time of peak concentration of drug. The importance of understanding the pharmacokinetic and pharmacodynamics effects in the individual patient must be stressed, since most studies have reported

only mean data, but physicians treat individuals. Considering that one patient achieved a plasma norepinephrine concentration of $>1300 \text{ pg ml}^{-1}$ at the time of peak nifedipine concentration in the Coracten XL group, this concentration could lead to a significant haemodynamic effect in this individual, which could easily be missed by the practising primary care physician. Moreover, in the present healthcare environment patients going to their pharmacists to renew their prescriptions may receive a different once-a-day nifedipine than what their physician originally prescribed, perhaps due to acquisition cost differences, or formulary listings. Regulatory authorities examine the comparative pharmacokinetics of new market entry once daily nifedipines compared with the existing marketed formulation, but do not routinely request detailed pharmacodynamics data. The results of this study therefore become relevant to determine if various once-daily formulations of nifedipine are therapeutically interchangeable. This study, taken together with the more detailed pharmacokinetic analysis of Schug *et al.*, suggests that the pharmacokinetics and pharmacodynamics of the Coracten XL are significantly different than Nifedipine GITS after a meal [1]. Patients do not routinely take their medication at exactly the same time of day or in relation to food [16, 17]. Therefore these data become relevant for regulators, physicians and pharmacists to caution patients adequately not to switch between formulations of once-a-day nifedipines.

Conclusion

Use of different formulations of long-acting nifedipine influence the noradrenergic and haemodynamic response, especially at the time of switching formulations.

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