Journal of Human Hypertension (2002) 16, 805–813

www.nature.com/jhh

ORIGINAL ARTICLE

Persistence of the antihypertensive efficacy of amlodipine and nifedipine GITS after two 'missed doses': a randomised, double-blind comparative trial in Asian patients

I Ongtengco[1], D Morales[2], J Sanderson[3], Z-R Lu[4], LJ Beilin[5], V Burke[5], IB Puddey[5], S Tanomsup[6], H Dayi[7], P Rahardjo[8], Dato R Zambahari[9], C-Y Chen[10], AA Soenarta[11], P Buranakitjaroen[12], C Tan[13], TK Soon[14] and D-J Wu[15]

[1]*St Luke's Medical Center, Quezon City, Philippines;* [2]*Manila Doctors Hospital, Manila, Philippines;* [3]*The Chinese University of Hong Kong, Hong Kong;* [4]*Xian Medical University, First Affiliated Hospital, Xian, China;* [5]*University Department of Medicine, University of Western Australia, Perth, Australia;* [6]*Ramathibodi Hospital, Mahidol University, Bangkok, Thailand;* [7]*Beijing Chaoyang Hospital, Beijing, China;* [8]*Rumah Sakit Cipto Mangunkusumo, Jakarta, Indonesia;* [9]*Institute Jantung Negara, Kuala Lumpur, Malaysia;* [10]*Kuang Tien General Hospital, Taichung, Taiwan;* [11]*Rumah Sakit Harapan Kita, Jakarta, Indonesia;* [12]*Siriraj Hospital, Mahidol University, Bangkok, Thailand;* [13]*University Hospital, Kuala Lumpur, Malaysia;* [14]*Changi General Hospital, Singapore;* [15]*Chung-Shan Medical and Dental College, Taichung, Taiwan*

Suboptimal management of hypertension is often a result of poor patient compliance in the form of missed doses of their antihypertensive medication. This multicentre, randomised, double-blind, parallel-group trial was designed to compare the persistence of the antihypertensive efficacy of the amlodipine and nifedipine gastrointestinal therapeutic system (GITS) after two 'missed doses', and also to compare the drugs' overall efficacy and safety in Asian patients with mild-to-moderate essential hypertension. Following a 2-week placebo run-in period, 222 patients were randomised to receive either amlodipine (5 mg daily, increased after 6 weeks if necessary to 10 mg daily, $n = 109$) or nifedipine GITS (30 mg daily, increased after 6 weeks if necessary to 60 mg daily; $n = 113$) for 12 weeks. A placebo was then substituted for further 2 days with continuous ambulatory blood pressure (BP) monitoring. The increases in the last 9 h of mean ambulatory BP on day 2 after treatment withdrawal were significantly less with amlodipine than with nifedipine GITS: 4.4 ± 7.0 *vs* 11.2 ± 11.3 mmHg for systolic BP ($P \leqslant 0.0001$) and 2.4 ± 6.3 *vs* 6.0 ± 6.0 mmHg for diastolic BP ($P \leqslant 0.0002$). Significant differences between the two drugs in mean 24-h ambulatory BP levels were already evident on day 1 after withdrawal, even though there were no significant differences on the final day of treatment. No differences in safety parameters were observed, and neither drug caused any serious or severe treatment-related adverse events. In conclusion, amlodipine provides greater protection than nifedipine GITS against loss of BP control following missed doses.
Journal of Human Hypertension (2002) **16,** 805–813. doi:10.1038/sj.jhh.1001485

Keywords: amlodipine; nifedipine GITS; essential hypertension; efficacy; medication compliance; missed doses

Introduction

The benefits of antihypertensive therapy in reducing the morbidity and mortality associated with mild-to-moderate hypertension are well established, and minimum acceptable targets for blood pressure (BP) control ($<140/<90$ mmHg) have been recommended in various national and international treatment guidelines.[1–3] In achieving these target levels, the importance of consistent 24-h BP control has been emphasized.[4] Indeed, it is well known that BP follows a circadian variation, usually (although not always) characterised by lowest values around midnight and highest values in the morning, and the

Correspondence: Dr I Ongtengco, Rm 105 Medical Arts Bldg, St Luke's Medical Center, E Rodriguez Sr Blvd, Quezon City, Philippines.

risk of cardiovascular events is greatest in the early hours of the morning if BP is not controlled at this time. Evidence of the benefits of consistent 24-h BP control has come from an important study that correlated regression of left ventricular hypertrophy (LVH) more closely with treatment-induced changes in 24-h ambulatory BP than with changes in clinic supine BP measurements.[5]

Despite the considerable body of evidence for the benefits of controlling elevated BP, the clinical management of hypertension is often inadequate.[6–8] A commonly encountered problem is less than optimal acceptance of therapy by patients, particularly if they are not able to detect any improvement in their quality of life, leading to lack of compliance with the prescribed regimen.[9–11] In fact, noncompliance with the treatment regimen, particularly in the first year of treatment, is one of the primary contributors to the large number of patients with uncontrolled hypertension,[7,11,12] and more than 50% of patients who fail to achieve the goal BP levels display suboptimal compliance rather than an inadequate regimen.[10] As noncompliance most commonly takes the form of missing at least one medication dose each week ('drug holidays'),[4,7] regimens that provide a sustained duration of effect beyond 24 h may offer advantages by protecting patients against loss of BP control when doses are inadvertently omitted.

A number of studies have investigated whether long-acting antihypertensives do indeed protect patients against loss of BP control following missed doses by deliberately inserting a placebo phase into a steady-state drug regimen to mimic this pattern of suboptimal compliance.[4] We employed this design in a multicentre study in Asian patients with mild-to-moderate essential hypertension to compare the persistence of the antihypertensive efficacy of two commonly used calcium antagonists, amlodipine and nifedipine gastrointestinal therapeutic system (GITS), by substituting a placebo at steady state. Both drugs have long durations of action and are administered once daily. In addition to studying the persistence of their antihypertensive efficacy after 'missed doses', we also sought to compare their overall efficacy and safety in an Asian hypertensive population.

Materials and methods

Study design

A randomised, double-blind, parallel-group clinical trial was undertaken at 14 centres in Southeast Asia: two each in China, Indonesia, Malaysia, Philippines, Taiwan and Thailand, and one each in Hong Kong and Singapore. The study was conducted in accordance with the ethical principles contained in the Declaration of Helsinki, and was approved by Ethics Review Committees at each site. All patients gave their written informed consent to participate in the study.

The trial was designed primarily to compare the duration of action of amlodipine with that of nifedipine GITS by withdrawing each drug after it had been given for 12 weeks and measuring the patients' BP for 72 h or more after the last dose. It was also designed to compare the overall efficacy and safety of the two agents in an Asian hypertensive population. The study design and visit schedule are shown in Figure 1.

Patients and medication

The patients enrolled were of Asian ethnicity and were between 26 and 75 years of age. All had newly diagnosed essential hypertension or a history of essential hypertension, but were not currently receiving antihypertensive medications (including herbal medicines, where applicable). Hypertension was defined as an average of two sitting diastolic

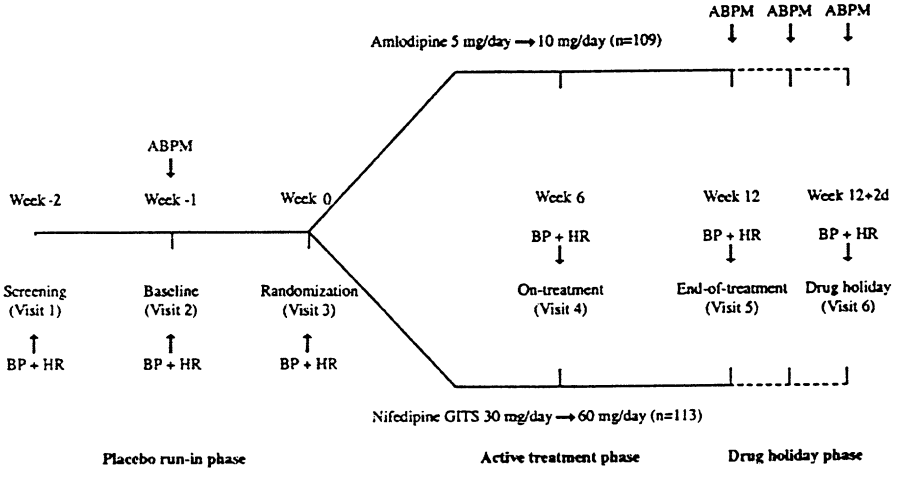

Figure 1 Study design and visit schedule: ABPM, 24-h ambulatory blood pressure monitoring; BP, blood pressure; HR, heart rate.

blood pressure (DBP) values of >95 and $\leqslant 115$ mmHg documented on two separate occasions at least 1 week apart (provided the difference was not >10 mmHg), and as a mean daytime (0600 to 2200) ambulatory DBP of >90 mmHg. Criteria for exclusion from the trial included a prior myocardial infarction, stroke, transient ischaemic attack, balloon dilatation of coronary arteries or coronary artery bypass operation within the previous 6 months, pregnancy or lactation, the presence of secondary, malignant or severe ($>200/>115$ mmHg) hypertension, angina pectoris, heart failure (New York Heart Association classes II–IV), serious arrhythmias or greater than first-degree heart block, clinically important hepatic or renal dysfunction, orthostatic hypotension, a history of drug or alcohol abuse, psychological/emotional disorders or other conditions that might interfere with the conduct of the study, and known hypersensitivity to calcium antagonists.

Following a full assessment at the initial screening visit, the patients entered a 2-week placebo run-in period, during which they received a dummy tablet of each of the trial medications once daily. At the end of this period, eligible patients were randomised via a computer-generated procedure to receive either amlodipine 5 mg or nifedipine GITS 30 mg once daily (at breakfast time) for the first active treatment period of 6 weeks. To maintain double-blind conditions, each group also received placebo tablets of the alternative medication so that all patients took two tablets per day. After 6 weeks, if the target DBP of $\leqslant 90$ mmHg had not been achieved, dosages of the two drugs could be increased, at the discretion of the investigator, to amlodipine 10 mg or nifedipine GITS 60 mg once daily (at breakfast time) for the second 6-week active treatment period—provided the patient had tolerated the initial dosage. No other antihypertensive medications were allowed.

At the end of the 12-week treatment phase, placebo tablets were substituted for the active drug in both groups and continued for a further 2 days ('drug holiday' phase). Office BP was measured with a standard sphygmomanometer in the sitting position (mean of two recordings after 5 min rest) and standing position (mean of two recordings). A 24-h ambulatory BP monitoring (ABPM) was recorded using a Spacelabs Ambulatory Blood Pressure Monitor (model 90207-30). Prior to the actual study conduct, the investigators underwent training on the installation, usage and reporting of ambulatory BP results.

Sitting and standing BP, heart rate (HR) and 24-h ABPM were measured at the time points indicated in Figure 1. All ABPM readings were analysed at the University of Western Australia by personnel who were blinded to the treatment allocation.

Standard haematology and biochemistry laboratory tests were performed at the initial screening and end-of-treatment visits.

Assessment of efficacy

The *Primary efficacy parameter* was the change in BP over the 'drug holiday' period, that is, the change in the last 9 h of mean ambulatory BP values between the end-of-treatment (week 12) and day 2 of the 'drug holiday' period. Differences in the last 9 h of mean ambulatory BP values were also measured between baseline (week −1) and day 2 of the 'drug holiday' period, and between baseline and end-of-treatment.

Secondary efficacy parameters included: (1) changes in mean 24-h ambulatory BP values between end-of-treatment and both day 2 and day 1 of the 'drug holiday' period; (2) changes in mean sitting clinic BP values between end-of-treatment and day 2 of the 'drug holiday' period and between baseline (randomisation) and end-of-treatment; (3) changes in mean 24-h ambulatory BP values during the daytime (0600 to 2200) and at night (midnight to 0600) between end-of-treatment and day 2 of the 'drug holiday' period, between baseline (week –1) and day 2 of the 'drug holiday' period, and between baseline and end-of-treatment; and (4) the 'nondipper' status, that is, the percentage of patients whose average night time ambulatory BP was not $\geqslant 10\%$ less than their average daytime ambulatory BP at baseline (week −1), end-of-treatment, and day 2 of the 'drug holiday'.

Assessment of safety

This was assessed via: (1) adverse events observed by the investigators or volunteered by patients at each study visit, regardless of a suspected causal relationship to the study medication; (2) clinically significant changes in physical examination findings; and (3) changes in standard laboratory test values requiring a change in drug dosage, discontinuation, or other interventions.

Statistical analysis

Analyses were performed on the intent-to-treat (ITT) patient population, which comprised all randomised patients who received at least one dose of study medication. All statistical tests were two-sided and a significance value of $P<0.05$ was applied using SAS® 6.12. Baseline demographic variables were reported as summary statistics (mean and s.d. for age, and body weight and frequency for sex) within each treatment group. The primary and secondary efficacy parameters were analysed using general linear models that provided for treatment, centre, and treatment-by-centre interaction effects. Treatment group differences were assessed using least-squares means (LS means) and contrast statements. 'Dipper' status was analysed using the Cochran–Mantel–Haenszel model with centre as the stratum variable.

Results

A total of 222 patients, all of Asian ethnicity, were considered eligible and were randomised to receive either amlodipine ($n=109$) or nifedipine GITS ($n=113$). All received at least one dose of the study medications and the ITT population therefore comprised 222 patients. As shown in Table 1, the two treatment groups did not differ markedly for any baseline characteristic, including coexisting disease states and concomitant medications. Mean doses of amlodipine and nifedipine GITS taken during weeks 1–6 of the treatment phase were 5.0 and 30 mg/day, respectively, while during weeks 6–12, 67% of the amlodipine and 53% of the nifedipine GITS patient were uptitrated to 10 and 60 mg/day, respectively.

During the study, 19 patients were withdrawn, 11 from the amlodipine group (all for reasons unrelated to the drug) and eight from the nifedipine GITS group (one because of an adverse event considered treatment-related and seven for reasons unrelated to the drug). A further two patients (one in each group) had <80% valid ambulatory BP recordings and were also excluded from the efficacy analyses. Thus, efficacy data were evaluable in 201 patients.

Table 1 Demographic characteristics of the patients studied (ITT population: *n*=222); all patients were of Asian ethnicity[a]

Characteristic	*Amlodipine (n=109)*	*Nifedipine GITS (n=113)*
Gender		
Males (*n*, %)	56 (51.4)	59 (52.2)
Females (*n*, %)	53 (48.6)	54 (47.8)
Age, years (mean ± s.d) [range]	50.2 (±9.44) [28–75]	50.6 (±8.91) [26–75]
Duration of hypertension, years (mean±s.d.) [range]	7.8 (±7.45) [0–32]	7.8 (±6.97) [0–31]
Mean (±s.d.) baseline sitting BP[b]		
Systolic (mmHg)	156.2 (±14.2)	155.3 (±15.1)
Diastolic (mmHg)	101.4 (±6.6)	102.1 (±7.2)
Coexisting disease states[c] (*n*, %)	39 (35.8)	45 (39.8)
Arthropathies	6 (5.5)	4 (3.5)
Diabetes mellitus	7 (6.4)	3 (2.7)
Ocular disorders	13 (11.9)	17 (15.0)
Upper respiratory tract disorders	1 (0.9)	3 (2.7)
Metabolic and immune disorders	9 (8.3)	7 (6.2)
Concomitant medications[c] (*n*, %)	49 (45.0)	43 (38.1)
Analgesics	19 (17.4)	16 (14.2)
Antibacterial drugs	7 (6.4)	10 (8.8)
Antihistamines	7 (6.4)	7 (6.2)
Anti-inflammatory/antigout drugs	14 (12.8)	20 (17.7)
Antihyperlipidaemic drugs	4 (3.7)	5 (4.4)
Vitamins	11 (10.1)	8 (7.1)

[a]*Patient distribution:* 42 from China, 25 from Hong Kong, 35 from Indonesia, 15 from Malaysia, 64 from Philippines, 8 from Singapore, 9 from Taiwan, and 24 from Thailand.
[b]At randomization; data shown are for patients who completed the study (amlodipine 98; nifedipine GITS 105).
[c]Most commonly occurring coexisting diseases or commonly taken concomitant medications are listed.

Efficacy outcome

Primary efficacy analyses: Differences in the last 9-h mean ambulatory BP values between the last day of active treatment and day 2 of the 'drug holiday' period in the two groups of patients are shown in Figure 2. For both systolic BP (SBP) and DBP, the increases that occurred following drug withdrawal in the amlodipine group were statistically significantly smaller than in the nifedipine GITS group (SBP, $P\leqslant 0.0001$; DBP, $P\leqslant 0.0002$) (Figure 2). Statistically significant differences between the two groups were also apparent for the decreases in the last 9-h mean ambulatory BP values from baseline (week –1) to day 2 of the 'drug holiday' period (SBP, $P\leqslant 0.0001$; DBP, $P\leqslant 0.0004$) (amlodipine: SBP -15.7 ± 11.8, DBP -8.9 ± 8.5; nifedipine GITS: SBP -8.6 ± 9.7, DBP -5.5 ± 6.0). However, there was no significant difference between the two groups in the decreases from baseline to the end-of-treatment visit.

Secondary efficacy analyses: Changes in mean 24-h ambulatory BP values between the last day of active treatment and day 2 of the 'drug holiday' period also showed statistically significant differences between the two groups, the increases following drug withdrawal being significantly smaller with amlodipine (Table 2). The difference between the two groups was already apparent by the first day of the 'drug holiday' period, as the rises in SBP and DBP were again significantly less with amlodipine on day 1 (SBP, $P\leqslant 0.002$; DBP, $P\leqslant 0.005$). Plots of the hourly mean ambulatory BP values over the 24-h period on day 2 of the 'drug holiday' and on the last day of active treatment (Figure 3) showed that the difference between the

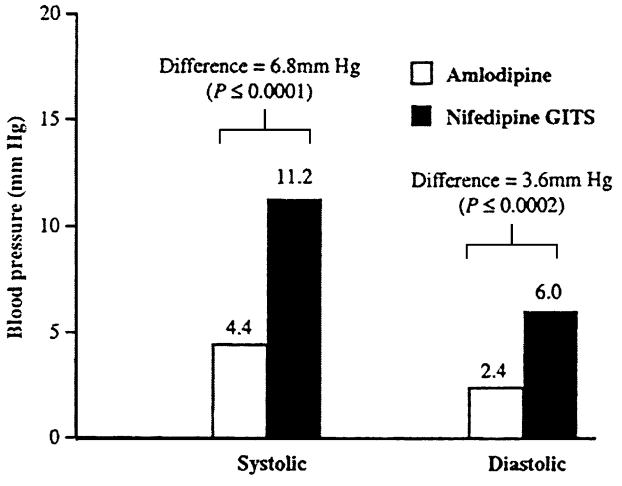

Figure 2 Rises in the last 9 h of ambulatory BP (mean ± s.d.) in the two patient groups between the end-of-treatment (week 12; visit 5) and day 2 of the 'drug holiday' (week 12+2 days; visit 6).

Table 2 Other ambulatory BP comparisons in evaluable patients (n=201) who completed the study[a]

Outcome analyses		*Change in BP between visits (mmHg)*		*Difference (A vs N)*
		Amlodipine (A) (n=97)	*Nifedipine GITS (N) (n=104)*	*(95% CI) [P-value]*
Rise in mean 24 h ambulatory BP after two	SBP	+4.8 (± 6.2)	+11.2 (± 9.9)	6.4 (4.2, 8.7) [0.0001]
missed doses *vs* end -of-treatment	DBP	+2.7 (± 5.2)	+6.3 (± 6.1)	3.6 (2.1, 5.2) [0.0001]
Rise in mean 24 h ambulatory BP after one	SBP	+2.6 (± 6.9)	+5.5 (± 6.9)	2.9 (1.1, 4.6) [0.002]
missed dose *vs* end-of-treatment	DBP	+1.4 (± 3.6)	+3.0 (± 4.4)	1.6 (0.5, 2.7) [0.005]
Rise in mean daytime[b] ambulatory BP after two	SBP	+5.1 (± 6.6)	+11.7 (± 9.8)	6.6 (4.2, 8.9) [0.0001]
missed doses *vs* end-of-treatment	DBP	+3.0 (± 5.3)	+6.6 (± 6.1)	3.6 (2.0, 5.2) [0.0001]
Rise in mean night time[b] ambulatory BP after two	SBP	+4.1 (± 8.3)	+10.4 (± 12.5)	6.3 (3.2, 9.3) [0.0001]
missed doses *vs* end-of-treatment	DBP	+2.4 (± 7.3)	+5.7 (± 8.0)	3.3 (1.1, 5.5) [0.0028]
Decrease in mean daytime[b] ambulatory BP at	SBP	−20.1 (± 12.0)	−21.8 (± 12.0)	−1.7 (−4.8, 1.4) [0.26]
end-of-treatment *vs* baseline	DBP	−11.7 (± 7.5)	−12.1 (± 7.1)	−0.4 (−2.3, 1.6) [0.72]
Decrease in mean night time[b] ambulatory BP at	SBP	−20.4 (± 14.9)	−18.3 (± 13.5)	2.1 (−1.9, 5.8) [0.442]
end-of-treatment *vs* baseline	DBP	−11.7 (± 9.7)	−10.2 (± 8.7)	1.5 (−1.1, 4.0) [0.381]

[a]The mean (± s.d.) SBP and DBP values shown for each treatment group are the differences between values recorded at the study visits indicated (baseline=visit 2 (week −1); end-of-treatment =visit 5 (week 12); one missed dose=day 1 of 'drug holiday' (visit 6: week 12+1 day); two missed doses=day 2 of 'drug holiday' (visit 6 week 12+2 days)).
[b]Daytime ambulatory BP=0600 to 2200; night time ambulatory BP=midnight to 0600.
A, amlodipine; N, nifedipine GITS; CI, confidence interval; DBP, diastolic blood pressure; SBP, systolic blood pressure.

two groups in terms of the divergence of SBP and DBP values on these days was most apparent in the early evening. Similar results were also seen for the first day of the 'drug holiday' period (data not shown).

Other analyses provided similar findings. Measurements of the mean sitting BP (data not shown) and of daytime (0600 to 2200) and night time (midnight to 0600) mean ambulatory BP (Table 2) showed significantly smaller increases in BP from the end-of-treatment to day 2 of the 'drug holiday', and significantly greater overall decreases from baseline to day 2 of the 'drug holiday' in the amlodipine group (data not shown), but there was no significant difference between the two drugs for the change in BP from baseline to end-of-treatment (Table 2).

There were no significant changes in the dipper/nondipper status during the trial.

Sitting HR did not change significantly in either arm from baseline to the end of active therapy (76.4 to 75.8 on amlodipine and 76.8 to 76.3 on nifedipine GITS).

Safety outcome

Safety data were available for all 222 patients randomised (ITT population). During the study, treatment was withdrawn in one patient from each group owing to a treatment-emergent adverse event. The patient in the amlodipine group experienced an unstable angina episode, but this was not considered related to the study drug by the treating physician. The patient in the nifedipine GITS group experienced generalised weakness, oedema, palpitation, muscle pain and shortness of breath, and this was assessed as drug related by the treating physician.

Adverse events considered causally related to the study medications were similar in distribution and occurred in a similar number of patients in each group: 16 (14.7%) receiving amlodipine and 16 (14.2%) receiving nifedipine GITS (Table 3). Most were mild in intensity and no serious or severe events classified as treatment-related occurred with either agent.

No consistent clinically important laboratory abnormalities were encountered during the trail.

Discussion

Although there is no definitive evidence from long-term, randomised, prospective studies, the optimal antihypertensive drug can, intuitively, be defined as one that achieves consistent BP control over a full 24-h dosage interval,[4] since such agents are probably better able to provide protection against whatever risk of sudden death, heart attack or stroke occurs with the abrupt increase of BP on arising from an overnight sleep. This has been recognised by the US Joint Committee on the Prevention, Detection, Evaluation and Treatment of High Blood Pressure (1997),[1] which has further defined the optimal antihypertensive agent as one that has at least 50% of its peak effect remaining at the end of 24 h. This is because noncompliance is commonplace in hypertension management, and patients often miss at least one dose of their medication each week. Thus, drugs with a sustained antihypertensive effect offer the advantage of activity beyond the end of the regular

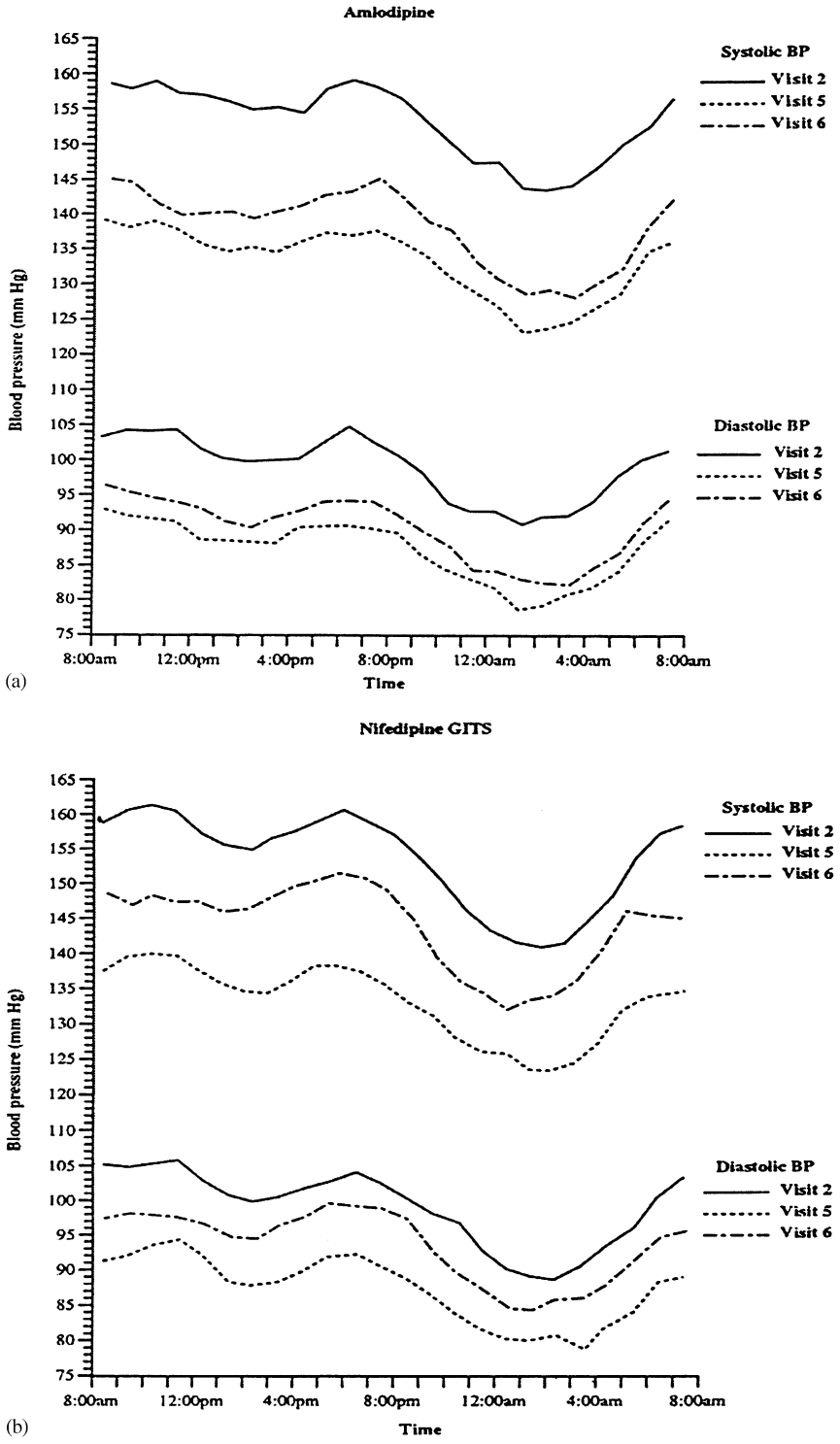

Figure 3 Hourly means of 24-h ambulatory SBP and DBP for (a) amlodipine and (b) nifedipine GITS measured at baseline (visit 2), end-of-treatment (visit 5), and day 2 of the 'drug holiday' (visit 6).

dosage interval that will, at least in part, compensate for the dosage omission.[1,4]

In this study, we investigated the validity of this contention by employing a randomised, double-blind study design that involved the substitution of a placebo for 2 days following 12 weeks of therapy with amlodipine and nifedipine GITS. The ensuing BP changes, over this simulated 'drug holiday', were measured by continuous ABPM. Amlodipine and nifedipine GITS were chosen for comparison as both are long-acting dihydropyridine-type calcium antagonists that are administered once daily, and both

Table 3 Adverse events considered causally related to the study medications recorded during the trial

Adverse event	*Amlodipine (n=109)*	*Nifedipine GITS (n=113)*
No. of patients experiencing adverse events (%)	16 (14.7)	16 (14.2)
Total no. of adverse events	27	31
Adverse events by body system[a]		
Body as a whole	6 (5.5)	6 (5.3)
Abdominal pain	0	2 (1.8)
Headache	6 (5.5)	2 (1.8)
Cardiovascular system	2 (1.8)	3 (2.7)
Palpitation	1 (0.9)	3 (2.7)
Digestive system	0	5 (4.4)
Constipation	0	2 (1.8)
Metabolic and nutritional	4 (3.7)	2 (1.8)
Oedema, peripheral	4 (3.7)	2 (1.8)
Musculoskeletal	0	1 (0.9)
Nervous system	4 (3.7)	4 (3.5)
Dizziness	3 (2.8)	2 (1.8)
Respiratory system	1 (0.9)	1 (0.9)
Skin and appendages	1 (0.9)	1 (0.9)
Urogenital system	2 (1.8)	2 (1.8)
Polyuria	1 (0.9)	2 (1.8)

[a]Individual adverse events occurring in $\geqslant 2$ patients in either treatment group are shown.

have proved to be effective and well tolerated in the management of essential hypertension.[13,14] Whereas amlodipine is an intrinsically long-acting agent with an elimination half-life of 35–50 h, nifedipine has a short half-life (approximately 2 h) but is formulated in a GITS that provides constant release of the drug over a 24-h period.

Our results in a hypertensive Asian population indicated that the rise in BP occurring over a 48-h 'drug holiday' period was significantly less in patients who received amlodipine (5–10 mg once daily) than in those who received nifedipine GITS (30–60 mg once daily). This was reflected in a significantly greater overall reduction in SBP and DBP from baseline (week −1) to day 2 of the 'drug holiday' in the amlodipine group (Table 2). Similarly, changes in the mean 24-h ambulatory BP between the last day of active treatment and the 'drug holiday' period were also significantly smaller in the amlodipine group on day 2, and this difference between the two drugs was already apparently on day 1.

In contrast to the 'drug holiday' findings, no differences in BP control between the groups could be demonstrated while they were still on therapy. From a pharmacokinetic perspective, BP control can be re-established quickly when nifedipine GITS medication is resumed. However, such BP fluctuations could potentially be harmful as suggested by the results from the European Lacidipine Study on Atherosclerosis (ELSA) trial.[15]

The first study to suggest a better therapeutic coverage of amlodipine *vs* nifedipine GITS in the case of missed doses was conducted in nine normotensive patients.[16] A subgroup (56 of 126 patients) from the Italian GITS study, comparing nifedipine GITS with placebo, was followed up to 36 h after the last dose. From 24 to 36 h, approximately half of the BP-lowering effect was lost.[17,18] A small open study (40 patients) using ABPM but no drug holiday suggested that patients were better controlled on amlodipine than nifedipine GITS from 5 to 10 am.[19]

Other studies in small numbers of patients that employed controlled drug withdrawal designs to compare the persistence of the antihypertensive efficacy of amlodipine and nifedipine GITS following simulated missed doses have described similar results to ours. In a double-blind crossover study in 27 Scottish patients with essential hypertension who received both amlodipine (5–10 mg daily) and nifedipine GITS (30–60 mg daily) for 12 weeks, mean arterial pressure (MAP) was maintained at a significantly lower level at 24–48 h and 48–72 h following simulated missed doses during weeks 8, 10 and 12 of therapy in amlodipine-treated patients in comparison with those treated with nifedipine GITS ($P<0.0001$).[20] However, when compliance was 'perfect', BP control was similar in the two groups. In an open crossover trial in 16 patients with untreated primary hypertension who received both amlodipine (5 mg daily) and nifedipine GITS (30 mg daily) for 10 weeks, SBP and DBP were significantly better reduced with amlodipine than with nifedipine GITS following simulated missed dose mainly because of a significantly lower BP during the 3–9 pm period ($145/92 \pm 15/10$ mmHg *vs* $149/95 \pm 13/11$ mmHg ($P<0.05$)) and the 3–9 am period ($131/84 \pm 11/4$ mmHg *vs* $138/88 \pm 14/8$ mmHg ($P<0.05$)).[21] In a single-blind study in 105 Spanish patients, amlodipine (5–10 mg daily) or nifedipine GITS (30–60 mg daily) was administered for 8 weeks followed by ABPM for 24 or 48 h after the last dose. The overall reduction in daytime and night time BP *vs* baseline was greater in those receiving amlodipine ($16.1 \pm 14.3/7.4 \pm 10.0$ mmHg *vs* $6.8 \pm 8.0/2.8 \pm 5.0$ mmHg), although only for the change in night time SBP was the difference between the two drugs statistically significant.[22] Studies employing similar designs to compare amlodipine with other antihypertensives have also reported the superiority of amlodipine in protecting against loss of BP control following simulated missed doses. In a double-blind study comparing amlodipine (mean dose 7.3 mg daily) and enalapril (mean dose 30.7 mg daily) given for 12 weeks to 30 Venezuelan patients, control of BP was maintained for up to 48 h after the last dose in those receiving amlodipine but was progressively lost in those treated with enalapril.[23] Similarly, in a double-blind study in 34 Canadian patients comparing amlodipine with diltiazem SR, the BP reductions achieved after 9 or 10 weeks of amlodipine therapy (5–10 mg daily) were still present on the second day after treatment withdrawal.

However, with diltiazem SR (90–180 mg twice daily), most of the BP reductions achieved had disappeared by the second day after withdrawal.[24]

Analyses of safety parameters in the Asian patients enrolled in this study showed that both amlodipine and nifedipine GITS were well tolerated. Treatment-related adverse events occurred in a similar number of patients ($n = 16$) in both groups and showed a similar distribution (Table 3). Most adverse events were mild in intensity and there were no serious or severe treatment-related events with either agent. Abnormal laboratory test values did not lead to the withdrawal of treatment in either group.

In summary, following controlled withdrawal at steady state, amlodipine was significantly more effective than nifedipine GITS in attenuating the resultant BP rise over the next 48 h. This indicates that amlodipine has a longer duration of antihypertensive action than nifedipine GITS and will provide greater protection against the loss of BP control that occurs following missed doses, which is the most common form of noncompliance in antihypertensive therapy.

Acknowledgements

This study was supported by Pfizer, Inc.

References

1 Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure. The Sixth Report of the US Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure. *Arch Intern Med* 1997; **157**: 2413–2446.
2 World Health Organization (WHO)–International Society of Hypertension (ISH). 1999. World Health Organization–International society of Hypertension Guidelines for the management of Hypertension. *J Hypertens* 1999; **17:** 151–183.
3 Ramsay L *et al*. Guidelines for management of hypertension: report of the third working party of the British Hypertension Society. *J Hum Hypertens* 1999; **13:** 569–592.
4 Meredith PA. The importance of sustained blood pressure control. *J Cardiovasc Pharmacol* 2000; **35** (Suppl 3)**:** S7–S11.
5 Mancia G *et al*. for the SAMPLE Study Group. Ambulatory blood pressure is superior to clinic blood pressure in predicting treatment-induced regression of left ventricular hypertrophy. *Circulation* 1997; **95:** 1464–1470.
6 McInnes GT. Integrated approaches to management of hypertension: promoting treatment acceptance. *Am Heart J* 1999; **138** (part 2): 252–255.
7 Burnier M. Long-term compliance with antihypertensive therapy: another facet of chornotherapeutics in hypertension. *Blood Press Monit* 2000; **5** (Suppl 1): S31–S34.
8 Trilling JS, Froom J. The urgent need to improve hypertension care. *Arch Fam Med* 2000; **9:** 794–801.
9 Williams GH. Assessing patient wellness: new perspectives on quality of life and compliance. *Am J Hypertens* 1998; **11** (Part 2): 186S–191S.
10 Rudd P. Compliance with antihypertensive therapy: raising the bar of expectations. *Am J Manag Care* 1998; **4:** 957–966.
11 Mallion JM *et al*. Compliance, electronic monitoring and antihypertensive drug. *J Hypertens* 1998; **16** (Suppl 1): S75-S79.
12 Payne KA, Esmonde-White S. Observational studies of antihypertensive medication use and compliance: is drug choice a factor in treatment adherence? *Curr Hypertens Rep* 2002; **2:** 515–524.
13 Haria M, Wagstaff AJ. Amlodipine: a reappraisal of its pharmacological properties and therapeutic use in cardiovascular disease. *Drugs* 1995; **50:** 560–586.
14 Brogden RN, McTavish D. Nifedipine gastrointestinal therapeutic system (GITS). A review of its pharmacodynamic and pharmacokinetic properties and therapeutic efficacy in hypertension and angina pectoris. *Drugs* 1995; **50:** 495–512.
15 Mancia G *et al*. Relation between blood pressure variability and carotid artery damage in hypertension: baseline data from the European Lacidipine Study on Atherosclerosis. *J Hypertens* 2001; **19:** 1981–1989.
16 Ueda S *et al*. A comparative assessment of the duration of action of amlodipine and nifedipine GITS in normotensive subjects. *Br J Clin Pharmacol* 1993; **36:** 561–566.
17 Zanchetti A *et al*. Antihypertensive effects of nifedipine gastrointestinal therapeutic system on clinic and ambulatory blood pressure in essential hypertensives. *J Hypertens* 1993; **11** (Suppl 5): s334–s335.
18 Zanchetti A *et al*. Antihypertensive effects of nifedipine GITS on clinic and ambulatory blood pressure in essential hypertensives. *High Blood Press* 1994; **3:** 45–56.
19 Ferruci *et al*. 24-blood pressure profiles in patients with hypertension treated with amlodipine or nifedipine GITS. *Clin Drug Invest* 1997; **13**(Suppl 1): 67–72.
20 Elliott HL. Persistence of antihypertensive efficacy after missed doses: comparison of amlodipine and nifedipine GITS [abstract]. *J Hypertens* 1997; **15**(Suppl 4): 8B7.
21 Nussinovitch N, Rosenberg G, Peleg E, Rosenthal T. A comparative crossover evaluation of amlodipine and nifedipine GITS before and after a missed dose: 48-h blood pressure profiles. *Am J Hypertens* 2002; **15:** 580–582.
22 Motero J *et al*. Long acting calcium channel blockers in hypertension. Amlodipine *vs* nifedipine GITS comparative study [abstract]. *Am J Hypertens* 1998; **11:** 69A.
23 Hernandez-Hernandez R *et al*. The effects of a missing dose of enalapril versus amlodipine on ambulatory blood pressure. *Blood Press Monit* 1996; **1:** 121–126.
24 Leenen FH, Fourney A, Notman G, Tanner J. Persistence of anti-hypertensive effect after 'missed doses' of calcium antagonist with long (amlodipine) *vs* short (diltiazem) elimination half-life. *Br J Clin Pharmacol* 1996; **41:** 83–88.

Appendix

Members of the study group who conducted this trial were:

China: *Principal investigators:* Hu Dayi, Beijing Chaoyang Hospital, Beijing; Zhuo-Ren Lu, Xian Medical University First Affiliated Hospital, Xian. *Co-investigators:* Zhao Xiuli, Xu Zhimin, Liu Xiaohui, Cui Liang, Beijing Chaoyang Hospital, Beijing; Xue Xiaolin, Yuan Zuyi, Wang Dongqi, Qu Yi, Xian Medical University First Affiliated Hospital, Xian. *Study coordinators:* Yin Rongxiu, Beijing Chaoyang Hospital, Beijing; Guo Ning, Min Hui-e, Xian Medical University First Affiliated Hospital, Xian.

Hong Kong: *Principal investigator:* John Sanderson, The Chinese University of Hong Kong, Hong Kong. *Co-investigator:* Brian Tomlinson, The Chinese University of Hong Kong, Hong Kong. *Study Coordinator:* Wong Sau Ying, The Chinese University of Hong Kong, Hong Kong.

Indonesia: *Principal investigators:* Pudji Rahardjo, Rumah Sakit Cipto Mangunkusumo, Jakarta; *Arieska Ann Soenarta*, Rumah Sakit Harapan Kita, Jakarta. *Co-investigators:* Lucky Azizah Bawazier, Rumah Sakit Cipto Mangunkusomo, Jakarta; Santoso Karo-karo, Ismoyo Sunu, Rumah Sakit Harapan Kita, Jakarta. *Study coordinators:* Nanit Rahardjo, Rumah Sakit Cipto Mangunkusomo, Jakarta; Lasmaria Sitorus, Rumah Sakit Harapan Kita, Jakarta.

Malaysia: *Principal investigators:* Dato Robaayah Zambahari, Institute Jantung Negara, Kuala Lumpur; Christina Tan, University Hospital, Kuala Lumpur. *Co-investigators:* Na Boon Seng, Lam Kai Huat, Institute Jantung Negara, Kuala Lumpur; Chia Yook Chin, Chua Chin Teong, Lang Chim Choy, University Hospital, Kuala Lumpur. *Study coordinators:* Chia See Moi, Fong Chew Khew, Institute Jantung Negara, Kuala Lumpur; Tan Chan Soo Looi, University Hospital, Kuala Lumpur.

Philippines: *Principal investigators:* Dante Morales, Manila Doctors Hospital, Manila; Isabelo Ongtengco, St Luke's Medical Center, Quezon City. *Co-investigators:* Rody Sy, Rafael Castillo, Dennis Donor, Philip Chua, Manila Doctor's Hospital, Manila; Abondino Yunque, Michael Mercier Enriquez, St Luke's Medical Center, Quezon City. *Study coordinators:* Dannette Marbella, Manila Doctor's Hospital, Manila; Beverly Anne Callejo, St. Luke's Medical Center, Quezon City.

Singapore: *Principal investigator:* Tan Kok Soon, Changi General Hospital. *Co-investigator:* Woon Voon Ching, Changi General Hospital. *Study Coordinator:* Yew Lay Hwa, Changi General Hospital, Singapore.

Taiwan: *Principal investigators:* Chung-Yin Chen, Kuang-Tien General Hospital, Taichung; Der-Jinn Wu, Chung-Shan Medical and Dental College, Taichung. *Co-investigators:* Shih-Chung Huang, Mau-Rem Lin, Kuang Tien General Hospital, Taichung; Kwo-Chang Ueng, Chung-Shan Medical and Dental College, Taichung. *Study coordinators:* Chiao-Ling Chang, Kuang-Tien General Hospital, Taichung; Miao-Chi Chiu, Chung-Shan Medical and Dental College, Taichung.

Thailand: *Principal investigators:* Supachai Tanomsup, Ramathibodi Hospital, Mahidol University, Bangkok; Peera Buranakitjaroen, Siriraj Hospital, Mahidol University, Bangkok. *Co-investigators:* Suchet Takdhada, Ramathibodi Hospital, Mahidol University, Bangkok; Meta Phoojaroenchanachai, Siriraj Hospital, Mahidol University, Bangkok. *Study coordinators:* Nongluck Intarayota, Ramathibodi Hospital, Mahidol University, Bangkok; Surachai Saravich, Siriraj Hospital, Mahidol University, Bangkok.