A comparative assessment of the duration of action of amlodipine and nifedipine GITS in normotensive subjects

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- 1 This study in normotensive subjects compared the duration and consistency of action of amlodipine (5 mg) and nifedipine GITS (60 mg) by assessment of the attenuation of pressor responses to noradrenaline and angiotensin II.
- 2 Both drugs significantly attenuated pressor responses to both vasoconstrictors at 6 and 24 h post-dose with rightward shifts of up to 2.3-fold in the dose-response curves.
- 3 There was significantly less pharmacokinetic variability with amlodipine: for example, intra-subject variability was 33% with amlodipine and 59% with nifedipine GITS.
- 4 There were no significant differences in the pressor dose ratios up to 48 h post-dose with amlodipine whereas there was a significant and progressive reduction in the pressor dose ratios with nifedipine.
- 5 These results suggest that both drugs are broadly comparable as once daily treatments but amlodipine displayed less intra- and inter-subject variability and provided a significantly more sustained effect with a reserve of pharmacological activity up to 48 h post-dose.

Keywords amlodipine nifedipine GITS pressor responses

Introduction

Once daily dosage regimens are considered desirable for the long term drug treatment of hypertension, particularly in the interests of patient convenience and compliance [1, 2]. Since symptomatic adverse effects are additional factors which may compromise drug compliance, long-acting calcium antagonist drugs which avoid rapid fluctuation in vasodilator activity [3] are thought to be more likely to promote acceptance by the patients on the basis of sustained 24 h efficacy and a reduced incidence of symptomatic side effects [4, 5].

Although calcium antagonist drugs have been widely used for the treatment of hypertension and ischaemic heart disease for many years, the majority have the disadvantage of a multiple daily dosing requirement because of their short elimination half-lives [3]. Development of a long-acting calcium antagonist has depended on new agents with intrinsically long half-lives and durations of action (e.g. amlodipine) or on long-acting formulations of established drugs (e.g. nifedipine GITS) [6, 7]. Thus, both these types of agent are expected to be once-a-day treatments for patients with hypertension and ischaemic heart disease.

Several studies have shown that calcium antagonist drugs interfere in man with the pressor responses to adrenergic and nonadrenergic vasoconstrictor agents

[8, 9, 10]. Therefore, it is possible to assess the time course and magnitude of the antihypertensive/vasodilator activity of a calcium antagonist drug by measurement of its effects on vascular responsiveness in normotensive subjects [11, 12, 13]. The fundamental aim of this study was a comparative assessment of the duration and consistency of action of amlodipine and nifedipine GITS by measurement of the extent of the attenuation of the pressor responses to noradrenaline and angiotensin II.

Methods

Subjects

Nine healthy, normotensive males (aged 19 to 35 years) gave written informed consent for their participation in the study. They had no history of serious ill-health and none was taking any regular medication including over-the-counter preparations during 1 month prior to the study. Physical examinations, routine biochemical and haematological tests, and electrocardiography on their screening visits revealed no abnormalities. Exclusion

criteria included history of alcoholism, drug abuse, and psychological problems that were likely to invalidate informed consent. The study received prior approval from the West Ethical Committee of the Greater Glasgow Health Board.

Study design

This study comprised three treatment phases; placebo, amlodipine 5 mg daily, and nifedipine GITS 60 mg daily. In a double-blind, cross-over, randomised, balanced design, each subject took each treatment for 12 days. There were 2 week washout periods between treatment phases.

On days 10, 11, 12 of each phase, subjects reported to the Clinical Investigation Research Unit (CIRU) at 08.00 h for supervised drug administration. On day 12, the first pressor study was undertaken 6 h after the final dose and was repeated again 24 and 48 h after the final dose.

Pressor infusion studies

Details of this method have been described previously [11, 12, 13]. Subjects reported to the CIRU at the same time on each study day and received pressor infusions of noradrenaline (NA) and angiotensin II (AII). The sequence of the pressor infusions was randomised but for each individual remained constant throughout the study. Each infusion was administered with incremental dosage steps, each of 8 min duration, from $0.025 \mu\text{g kg}^{-1} \text{min}^{-1}$ for NA and from $1.0 \text{ ng kg}^{-1} \text{min}^{-1}$ for AII to produce a progressive controlled rise of 20–25 mm Hg mean arterial pressure. The maximum permissible increases, for safety reasons, were 45 mm Hg systolic and 30 mm Hg diastolic pressure. Blood pressure was measured minute-by-minute throughout the infusion by semiautomatic sphygmomanometer (Datascope, U.S.A.).

The pressor response values for systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP) and heart rate (HR) were calculated for each dose increment as the mean of the final 5 min recordings at each dose of vasoconstrictor. Response i.e. change from baseline blood pressure was plotted against log-dose and then adapted to a quadratic function. The MAP response was used for AII but, because the residual sum of squares was better, SBP was used for NA. PD_{20} values were calculated from the individual

fits in each subject: for NA, PD_{20} is the dose required to raise SBP by 20 mm Hg and for AII, it is the dose required to raise MAP by 20 mm Hg. The PD ratios for each vasoconstrictor were then calculated i.e. the ratio of the PD_{20} with the calcium antagonist to that with placebo.

Plasma concentrations of amlodipine nifedipine

Blood samples for the measurement of plasma concentrations of drugs were taken before and after each infusion study. Plasma concentrations of amlodipine were measured by gas chromatography with electron capture [14], with inter- and intra-assay coefficients of variation of 6.7 and 5.6%, respectively, and a limit of detection of 0.5 ng ml^{-1} . Plasma concentrations of nifedipine were measured by modified high performance liquid chromatography [15] using ultraviolet detection, with inter- and intra-assay coefficients of variation of 7.3% and 6.1%, respectively, and a limit of detection of 3.0 ng ml^{-1} .

Statistical analysis

Blood pressure and heart rate Differences in baseline blood pressure and heart rate between each treatment and each time point were analysed by two-way analysis of variance (ANOVA). When a significant difference was detected, 95% confidence intervals (CI) were calculated for the difference between the two groups with Bonferroni correction.

PD ratio To take account of the duplicate testing against placebo the required significance was adjusted to $P < 0.025$ and the time course for the PD ratio was analysed by two way ANOVA. 95% CI with Bonferroni correction were again calculated for significant differences.

Results

Blood pressure and heart rate

Table 1 shows baseline blood pressure and heart rate prior to the pressor infusions on each study day. There were no significant treatment-related differences in blood pressure and heart rate at any time.

Table 1 Baseline blood pressure (mm Hg) and heart rate (beats min^{-1}) prior to each pressor study

	Placebo			Amlodipine			Nifedipine GITS		
	SBP	DBP	HR	SBP	DBP	HR	SBP	DBP	HR
<i>6 h post-dose</i>									
Mean s.d.	116 $\pm$ 6	65 $\pm$ 8	63 $\pm$ 7	117 $\pm$ 7	66 $\pm$ 6	68 $\pm$ 7	115 $\pm$ 8	64 $\pm$ 6	64 $\pm$ 8
<i>24 h post-dose</i>									
Mean s.d.	115 $\pm$ 5	65 $\pm$ 8	59 $\pm$ 9	114 $\pm$ 7	66 $\pm$ 4	57 $\pm$ 7	114 $\pm$ 5	65 $\pm$ 8	60 $\pm$ 12
<i>48 h post-dose</i>									
Mean s.d.	114 $\pm$ 6	64 $\pm$ 7	57 $\pm$ 7	114 $\pm$ 9	64 $\pm$ 7	57 $\pm$ 8	113 $\pm$ 7	63 $\pm$ 9	56 $\pm$ 9

Pressor responses

Noradrenaline The mean values and 95% CI for the PD ratio for NA are shown in Figure 1. Both drugs significantly attenuated the pressor responses to NA at 6 and 24 h after the final doses.

With amlodipine, although the extent of the attenuation did not itself achieve statistical significance at 48 h after post-dose, there was no significant time-dependent reduction in the effect i.e. the PD ratios at 6, 24 and 48 h post-dose were not significantly different. With nifedipine GITS, not only did the attenuation fail to achieve statistical significance at 48 h but there was also a significant progressive reduction in its extent i.e. the PD ratios at 24 h and 48 h post-dose were significantly lower than that at 6 h post-dose (95% CI of differences; -0.1 to -1.1 , and -0.3 to -1.3 respectively; $P < 0.001$). Figure 2 shows the percent reduction with time in the PD ratio for NA.

Figure 1 Mean values and 95% CI for the PD ratios for noradrenaline at 6, 24, and 48 h after amlodipine (closed bar) and nifedipine GITS (open bar).

Figure 2 Percent reductions in the PD ratios for noradrenaline (relative to 6 h post-dose) after amlodipine (closed bar) and after nifedipine GITS (open bar). * = statistically significant.

Angiotensin II The mean values and 95% CI for the PD ratios for AII are shown in Figure 3. Both drugs significantly attenuated the pressor responses to AII at 6 h and 24 h post-dose but not at 48 h post-dose. There were no significant changes in the PD ratios at the different times after the final dose of amlodipine (as for NA) but the PD ratio at 48 h after the final dose of nifedipine GITS was significantly lower than both the 6 h and 24 h ratios (95% CI of differences; -0.3 to -0.7 , and -0.01 to -0.8 , respectively; $P < 0.001$). Figure 4 shows the percent reduction in the PD ratio for AII.

Concentration-effect relationship

Figure 5 shows the time course for the mean plasma concentrations of amlodipine and nifedipine. At 24 h post-dose the plasma concentrations of each drug were around 60% of the peak concentrations but at 48 h post-

Figure 3 Mean values and 95% CI for the PD ratios for angiotensin II after amlodipine (closed bar) and nifedipine GITS (open bar).

Figure 4 Percent reductions in the PD ratios for angiotensin II (relative to 6 h post-dose) after amlodipine (closed bar) and nifedipine GITS (open bar). * = statistically significant.

dose the plasma concentrations of nifedipine had decreased by a significantly greater extent to 19% of peak level whereas amlodipine had decreased to 45% of its peak level. The intra- and inter-subject variabilities were significantly less for amlodipine at respectively 33.3% ($P < 0.02$) and 27.3% ($P < 0.02$) compared with 58.9% and 45.3% for nifedipine.

Figures 6 and 7 show the relationships between PD ratios and plasma drug concentrations. For nifedipine,

Figure 5 Time course of plasma concentration of amlodipine (solid line) and nifedipine GITS (broken line). Data are shown as means and s.d.

Figure 6 Correlations between plasma concentrations of amlodipine and PD ratios for noradrenaline (a) and angiotensin II (b).

there were significant correlations between the plasma concentrations and the PD ratios for both NA ($r = 0.64$, $P < 0.01$) and AII ($r = 0.50$, $P < 0.05$). For amlodipine the correlations did not achieve statistical significance ($r = 0.42$ for NA and $r = 0.14$ for AII).

Discussion

At steady state, both amlodipine and nifedipine GITS significantly attenuated the blood pressure responses to noradrenaline and angiotensin II in normal volunteers. These results are entirely consistent with vasodilator/antihypertensive activity and with previous reports for other calcium antagonist drugs [8, 9, 10], including a recent report with amlodipine [16]. Assessment of the comparability of antihypertensive efficacy was not a component aim of this study but, although attenuation of both pressor responses was greatest 6 h after each drug, it tended to be more marked with nifedipine GITS. This finding suggests that these doses, amlodipine 5 mg and nifedipine GITS 60 mg, are not directly equivalent in terms of their maximum vasodilator/hypotensive effects.

Both drugs significantly attenuated the pressor responses to both vasoconstrictor substances at 24 h post dose confirming their 24 h durations of action. However, there was an important and significant differ-

Figure 7 Correlations between plasma concentration of nifedipine and PD ratios for noradrenaline (a) and angiotensin II (b).

ence between the two drugs in the time course of the changes in the magnitude of the PD ratios at 24 and 48 h post-dose. With amlodipine, there were no statistically significant differences in the PD ratios for 6, 24 and 48 h post-dose. For nifedipine GITS, however, there was a progressive reduction in the magnitude of the PD ratios: the PD ratios for NA at 24 h and 48 h were both significantly lower than that 6 h after the final dose and for AII the PD ratio at 48 h was significantly lower than those at 6 h and 24 h after the final dose. These results indicate that there is a more rapid offset of the effect of nifedipine GITS. It is likely that this reflects underlying pharmacokinetic characteristics since the rate of decrease in plasma levels of nifedipine between 24 and 48 h post-dose was more marked than that of amlodipine. Although nifedipine GITS releases drug at a constant rate for approximately 24 h, thereafter, once all the drug is released, plasma concentrations decline rapidly with a consequently rapid offset of drug effect. In contrast, the clearance of amlodipine continues at its intrinsically slow rate, with a gradual decline in plasma concentrations and gradual offset of drug effect.

The importance of the rate of changes in drug concentrations, in terms of the changes in the pharmacological effect of nifedipine, is highlighted by the identification of significant concentration-effect relationships with both NA and AII. Thus, the time course and magnitude of the 'vasodilator' effect of nifedipine GITS were clearly and directly related to the plasma concentrations of nifedipine. For amlodipine, the correlations between concentrations and effects were not statistically significant: this lack of a statistical correlation is more likely to reflect the relative lack of variability (intra- and inter-individual) in both the plasma amlodipine concentrations and the degree of attenuation maintained for up to 48 h. Thus, statistically significant correlations could not readily be confirmed across a

relatively narrow range of both plasma concentrations and PD ratios. It is possible that other factors apart from plasma drug levels may contribute to the persistence of the vascular effects of amlodipine: for example, there is a recent report suggesting that longterm treatment with calcium antagonist drugs may be associated with relatively greater attenuation of the response to angiotensin II even with unchanged plasma drug concentrations [17]. Although outwith the specific scope of this study the results, particularly for nifedipine, lend no support for such a concept.

In conclusion, the vasodilator activities of amlodipine and nifedipine GITS as once daily treatments appeared to be broadly comparable although the maximum effect of nifedipine tended to be greater than that of amlodipine which suggests that these particular doses were not directly equivalent. By simple extrapolation from the values at 6 and 24 h post-dose it appears that about 40 mg nifedipine GITS (35–44 mg) would be equivalent to 5 mg amlodipine. However, the drug concentrations and the overall effects of amlodipine were better sustained across 24 h with significantly less inter- and intra-subject variability. This more 'smoothly' sustained activity of amlodipine may be additionally beneficial in the treatment of hypertension since the extent of the variability in blood pressure, independently of the absolute level, has been correlated with end organ damage in hypertensive patients [18]. Finally, the results at 48 h post-dose suggest that amlodipine may be a better choice than nifedipine GITS in patients who display poor compliance which has been reported in up to 40% of patients [19] because, even after a missed dose, there was no significant decline in the degree of pressor attenuation. Further investigations are obviously required with comparable antihypertensive doses to clarify the long term clinical relevance of these differential features.

References

- 1 Kruse W, Eggert-Kruse W, Rampmaier J, Runnebaum B, Weber E. Dosage frequency and drug-compliance behaviour — a comparative study on compliance with a medication to be taken twice or four times daily. *Eur J clin Pharmac* 1990; **41**: 589–592.
- 2 Windmer RB, Cadoret RJ, Troughton E. Compliance characteristics of 291 hypertensive patients from a rural midwest area. *J Fam Pract* 1983; **17**: 619–625.
- 3 Stone PH, Antman EM, Mullar JE, *et al.* Calcium channel blocking agents in the treatment of cardiovascular disorders. Part II: hemodynamic effects and clinical application. *Ann Intern Med* 1980; **93**: 886–904.
- 4 Pedersen OL, Mikkelsen E, Christensen NJ, *et al.* Effect of nifedipine on plasma renin, aldosterone, and catecholamine in arterial hypertension. *Eur J clin Pharmac* 1979; **15**: 235–240.
- 5 Muller FB, Bolli P, Linder L, *et al.* Calcium antagonists and the second drug for hypertensive therapy. *Am J Med* 1985; **81** (Suppl 6A): 25–29.
- 6 Swanson DR, Barclay BL, Wong PSL, Theeuwes F. Nifedipine gastrointestinal therapeutic system. *Am J Med* 1987; **83** (Suppl. 6B): 3–9.
- 7 Abernethy DR. Amlodipine: pharmacokinetic profile of a low-clearance calcium antagonist. *J cardiovasc Pharmac* 1991; **17** (Suppl 1): S4–S7.
- 8 Elliott HL, Pasanisi F, Sumner DJ, Reid JL. The effect of calcium channel blockers on α_1 - and α_2 -adrenoceptor-mediated vascular responsiveness in man. *J Hypertension* 1985; **3** (Suppl. 3): S235–S237.
- 9 Pasanisi F, Elliott HL, Meredith PA, Sumner DJ, Reid JL. Effect of calcium channel blockers on adrenergic and nonadrenergic vascular responses in man. *J cardiovasc Pharmac* 1985; **7**: 1166–1170.
- 10 Murphy MB, Brown MJ, Scriven AJ, Heavey DJ, Dollery CT. Nifedipine and α adrenoceptor antagonism. *Clin Pharmac Ther*, 1984; **36**: 745–749.
- 11 Sumner DJ, Elliott HL, Reid JL. Analysis of the pressor dose response. *Clin Pharmac Ther* 1982; **32**: 450–458.
- 12 Sumner DJ, Elliott HL. The pressor dose-response in clinical cardiovascular pharmacology. *Br J clin Pharmac* 1987; **23**: 499–503.
- 13 Sumner DJ, Elliott HL, Vincent J, Reid JL. A pragmatic approach to the pressor dose response as an index of vascular reactivity and adrenoceptor function in man. *Br J clin Pharmac* 1987; **23**: 505–510.
- 14 Beresford AP, Macras PV, Stopher DA, Wood BA.

- Analysis of amlodipine in human plasma by gas chromatography. *J Chromatogr Biomed Appl* 1987; **420**: 178–183.
- 15 Waller DG, Renwick AG, Grunchy BS, George CF. The first pass metabolism of nifedipine in man. *Br J clin Pharmac* 1984; **18**: 951–954.
 - 16 Donati L, Buhler FR, Beretta-Piccoli C, Kusch F, Heinen G. Antihypertensive mechanism of amlodipine in essential hypertension: Role of pressor reactivity to norepinephrine and angiotensin II. *Clin Pharmac Ther* 1992; **52**: 50–59.
 - 17 Donnelly R, Elliott HL, Howie CA, Sumner DJ, Reid JL. Vascular pressor responses in treated and untreated essential hypertension. *J cardiovasc Pharmac* 1990; **16**: 191–196.
 - 18 Parati G, Pomidossi G, Albini F, Malaspina D, Mancia G. Relationship of 24 h blood pressure mean and variability to severity of target-organ damage in hypertension. *J Hypertension* 1987; **5**: 93–98.
 - 19 Rudd P, Ahmed S, Zachary V, Barton C, Bonduelle D. Improved compliance measure: applications in ambulatory hypertensive drug trial. *Clin Pharmac Ther* 1988; **48**: 676–685.

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