Letter to the Editor

A Comparative Crossover Evaluation of Amlodipine and Nifedipine GITS Before and After a Missed Dose: 48-h Blood Pressure Profiles

Despite good pharmacologic control of blood pressure (BP), the untoward effects of noncompliance and missed doses have become a matter of concern, evidenced by the high frequency of deviations from prescribed treatment.¹ Missing one or more days of medication on these “drug holidays” can disrupt the steady level of the drug and lead to rebound reactions when the dose is suddenly stopped, and restarting the full dose of the drug can evoke exaggerated effects.² A number of ways to compensate for these missed doses have been suggested, including antihypertensive drugs with 36, 48, and even 72 h of action prescribed every 24 h.¹

Convinced that 36 or 48 h of BP monitoring is more informative regarding duration and consistency of action of antihypertensive drugs than 24-h monitoring,³ we used the longer monitoring to evaluate these parameters in two long-acting calcium channel blockers, amlodipine and nifedipine gastrointestinal therapeutic system (GITS), following a missed dose.

In this open crossover trial, 16 currently untreated primary hypertension patients entered an initial treatment period of 5 weeks of therapy with 5 mg of amlodipine or 30 mg of nifedipine GITS once daily, after which they were switched to the other drug for another period of 5 weeks. No other concomitant antihypertensive drugs were allowed. The participants’ initial allocation to amlodipine or nifedipine GITS was randomized. A single 48-h ambulatory BP monitoring (ABPM), in which no study drug was given after the first 24 h (to simulate a dose omission by a poorly compliant patient), was recorded at the end of each 5-week phase. An accutracker (DX-Suntech Medical Instruments Inc., Eyncham Oxon, UK) using Korotkoff sounds was used. Pressure accuracy meets the standards of the Association for the Advancement of Medical Instrumentation (AAMI). For ABPM analyses, each 24 h was divided into four intervals that coincide with physiologic diurnal changes: 3:00 AM to 9:00 AM, 9:00 AM to 3:00 PM, 3:00 PM to 9:00 PM, and 9:00 PM to 3:00 AM.

The mean systolic BP (SBP) values were significantly lower with amlodipine than with nifedipine GITS during the entire first 24 h (135 ± 11 vs 137 ± 11 mm Hg, respectively, P < .05), which was mainly due to significant changes in the SBP during the 9:00 AM to 3:00 PM and 3:00 PM to 9:00 PM periods (140 ± 11 vs 142 ± 12, P < .04, and 136 ± 8 vs 139 ± 12 mm Hg, P = .001, respectively) (Fig. 1). During the first 24 h of ABPM, in which a study drug was administered, both drugs achieved similar mean values of diastolic BP (DBP), except from 3:00 PM to 9:00 PM, when the DBP was significantly lower with amlodipine than with nifedipine GITS (87 ± 7 vs 90 ± 10 mm Hg, respectively, P < .005) (Fig. 1). Throughout these first 24 h of ABPM, the heart rate with amlodipine was significantly lower than under nifedipine GITS (77 ± 7 vs 80 ± 7 beats/min, respectively, P = .001). This difference reached statistical significance of P < .05 in all time periods, save for the hours of 9:00 PM to 3:00 AM.

In the next (nondosed) 24 h, SBP and DBP were significantly better reduced with amlodipine than with nifedipine GITS: mean daily values 141/90 ± 13/9 vs 142/91 ± 10/9 mm Hg, respectively, P < .05, due largely to the contribution of the highly significant differences during the 3:00 PM to 9:00 PM period (145/92 ± 15/10 vs 149/95 ± 13/11 mm Hg, respectively, P < .05) and the 3:00 AM to 9:00 AM period (131/84 ± 11/4 vs 138/88 ± 14/8 mm Hg, respectively, P < .05). During these nondosed 24 h there was no significant difference in heart rate between amlodipine and nifedipine GITS, except in the hours 9:00 AM to 3:00 PM. The drugs were equally well tolerated and no serious or adverse events were observed.

Indeed, both nifedipine GITS and amlodipine have demonstrated sustained antihypertensive efficacy and good tolerability in clinical trials,³,⁴ and both produced a smooth antihypertensive effect throughout the dose interval of 24 h by all methods used to evaluate this effect. They both significantly reduced sitting BP, and daytime, nighttime, and 24-h mean ambulatory BP. Using 24 to 36 h ABPM, the Italian Nifedipine GITS study³ found nifedipine GITS markedly reduced both SBP and DBP up to 30 to 36 h after the dose.⁵ Moreover, there were no significant changes in the heart rate at any time during the dose interval.

Because the degree of pressor attenuation did not decrease significantly even after a missed dose on this drug, the 48-h postdose data of Ueda et al⁶ suggest that amlodipine may be a better choice than nifedipine GITS in patients who display the poor compliance associated with failure to reach the therapy target.⁷ According to Elliott,⁸ both amlodipine and nifedipine GITS controlled BP when compliance was perfect, whereas missed doses resulted in significant loss of control with nifedipine GITS but not with amlodipine. When multivariate analysis was applied to ABMP data, amlodipine had greater antihypertensive efficacy than nifedipine GITS in terms of SBP and DBP reductions between 4:00 AM to 11:00 PM (P < .02 vs nifedipine GITS),⁴ Biston et al⁹ found that amlodipine’s duration of action was longer than 24 h, and 3 days of missed treatment did not significantly raise patients’ BP.

Our study, like the one of Ferrucci et al,⁵ evaluated the
effects of both nifedipine and amlodipine during the early morning hours, when there is an increased incidence of cardiovascular accidents. Similar to the data of Hernandez et al,1 Smilde10 and Leenen et al,11 our findings document that patients receiving amlodipine are protected during the early morning hours even when they miss a dose. These findings confirm previous studies6 in which both drugs were broadly comparable as once daily treatments, but amlodipine displayed less intra- and intersubject variability and provided a significantly more sustained effect with a reserve of pharmacologic activity up to 48 h after dose. Both these drugs sustain smooth blood concentrations and BP response over a steady-state dosage interval. But, research has shown that amlodipine, with its intrinsic long half-life (30 to 50 h in the human body),12 maintains an antihypertensive effect for at least 48 h, whereas response to nifedipine GITS starts to wane after 30 h as the drug formulation is exhausted and eliminated from the body. The persistently lower heart rate with amlodipine in the immediate hours after dosing might stem from lesser sympathetic activation; the fact that maximal plasma concentration is reached 9 h after taking the drug means a slow increase in amlodipine’s blood levels after each dose.12 The absence of an increase in norepinephrine levels after administration of nifedipine GITS suggests lesser activation of the sympathetic system. Tachycardia was also not observed in the International Nifedipine GITS: Intervention as a Goal in Hypertension Treatment study13 during treatment with nifedipine GITS, and acute administration of both dihydropyridines increased norepinephrine levels only in patients on amlodipine.

De Champlain et al,14 on the other hand, found a reduction in epinephrine levels after administration of both nifedipine GITS and amlodipine, suggesting inhibition of epinephrine release during treatment with the two dihydropyridines. We conclude that after a missed dose, amlodipine provides better SBP and DBP reduction than nifedipine GITS during times of natural circadian BP increase: the early evening hours and the high-risk early morning hours. Nevertheless, in an effort to improve com-

**FIG. 1.** Systolic (SBP) and diastolic (DBP) blood pressure during 48-h BP monitoring of patients rotating between nifedipine and amlodipine.
Compliance it is not worthwhile to encourage missed dosages of any drug.

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References