Once-Daily Monotherapy of Hypertension with Nifedipine Sustained Release (20mg to 100mg)

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Summary

A 2-centre double-blind randomised clinical study was conducted to evaluate the efficacy and tolerability of fixed doses of a new sustained release (SR) formulation of nifedipine compared with placebo in 207 patients with mild to moderate uncomplicated essential hypertension. After a 3- to 6-week placebo washout period, patients were randomised to receive either placebo, nifedipine SR 20mg, nifedipine SR 50mg or nifedipine SR 100mg. All doses were taken once daily in the morning without food. Among the 157 patients who completed 6 weeks of active therapy, the mean diastolic blood pressure reductions from baseline at 24 hours postdose were 5.3mm Hg, 9.3mm Hg, 9.7mm Hg and 11.1mm Hg in the placebo and nifedipine SR 20mg, 50mg and 100mg groups, respectively (p < 0.01). Nifedipine SR given in fixed doses once daily produced a relatively uniform antihypertensive effect throughout the 24-hour dosing interval, as determined by ambulatory blood pressure monitoring. All 3 dosages of nifedipine SR were generally well tolerated. A major finding of this study was the efficacy and safety of the once-daily 20mg dose.

Hypertension, defined as blood pressure ≥ 140/90mm Hg, is now estimated to affect about 58 million Americans (Joint National Committee 1988). Compared with normotensives, patients with hypertension are at an increased risk of developing coronary artery disease (CAD) and stroke (Joint National Committee 1988). A variety of effective pharmacological agents are currently available for the treatment of high blood pressure, and there is ample evidence that normalisation of blood pressure significantly reduces fatal and nonfatal cardiovascular disease and stroke (Collins et al. 1990; MacMahon et al. 1986; Working Group 1987). However, drug therapy is not free of adverse effects, and some agents are more frequently associated with such effects than others. In addition, the selection of an antihypertensive agent for an individual patient is often based on cost effectiveness, the likely effects of the drug on the patient's quality of life (particularly on concurrent illnesses and exercise tolerance), or the likelihood of compliance with the prescribed drug regimen (Cummings et al. 1991).

The calcium channel blockers verapamil, diltiazem and nifedipine, also referred to as calcium antagonists and which differ in chemical structure and pharmacological properties, have proved to be
safe and effective antihypertensive agents (Aoki et al. 1982; Cummings et al. 1991; Frishman et al. 1985, 1988; Joint National Committee 1988; Kaplan 1989; Opsahl et al. 1989). These drugs cause sodium diuresis and reduce systemic vascular resistance (Cummings et al. 1991; Kaplan 1989). Such properties make the calcium antagonists particularly suitable for the long term treatment of hypertension. However, verapamil, diltiazem and nifedipine have a short duration of action and immediate release formulations therefore require multiple daily dosing for adequate antihypertensive effects (Cummings et al. 1991). This is an undesirable property since it has been shown that compliance in general decreases with increased frequency of dosing, especially in hypertensive patients (Black 1988; Cramer et al. 1989; Eisen et al. 1990; Fujii & Akira 1985; Neal 1989; Pullar et al. 1988). This compliance problem in patients with high blood pressure may be due to the chronic nature of hypertension and its lack of symptoms. Older patients, who are frequently prescribed antihypertensive agents and are particularly vulnerable to the consequences of noncompliance, have the most difficulty with adhering to multiple dosing schedules (Eisen et al. 1990).

Nifedipine, the first commercially available calcium antagonist, has proved to be efficacious in the treatment of hypertension (Aoki et al. 1982; Cummings et al. 1991; Frishman et al. 1985, 1988; Kaplan 1989; Opsahl et al. 1989). However, it is a water-insoluble compound with a short elimination half-life (Cummings et al. 1991), usually necessitating administration 3 times daily. A formulation of nifedipine that combines the following properties would thus be highly desirable: reliable controlled release and absorption of nifedipine throughout the gastrointestinal (GI) tract, allowing for once-daily dosing; and complete disintegration in the GI tract without leaving a ‘ghost’ tablet of inert ingredients to be eliminated in the faeces, as occurs with some delayed release products. The latter property is a potential concern as one of the currently available formulations of nifedipine that does leave a ‘ghost’ remnant has been reported to cause gastric outlet obstruction (Prisant 1991). A new orally administered sustained release (SR) tablet has recently been developed that uses amorphous nifedipine in a complex hydrogel matrix system known as INDASTM (Insoluble Drug Absorption System) [Elan Corporation, Gainesville, Georgia]. The matrix is designed to erode gradually and completely in a controlled and programmed process during its passage through the GI tract and to release readily absorbable noncrystalline nifedipine at distal sites within the GI tract in a predictable fashion over a full 24-hour period.

A study was conducted to evaluate the antihypertensive efficacy and tolerability compared with placebo of 3 different doses (20mg, 50mg and 100mg administered once daily) of this new nifedipine SR formulation in patients with mild to moderate essential hypertension. Trough blood pressure measurements taken 23 to 25 hours after morning dose administration and ambulatory blood pressures over the 24-hour dosing interval were examined, as was the relationship between dose and antihypertensive effect over the range of doses studied.

**Methods**

A 2-centre double-blind placebo-controlled fixed-dose parallel group trial of sustained release nifedipine (Adalat® SR) given once a day to adult hypertensives was conducted. Men and nonpregnant, non-nursing women (either practising effective contraception or postmenopausal) between the ages of 21 and 70 years were eligible for enrolment. All patients were ambulatory, with mild to moderate essential hypertension, defined as an average supine diastolic blood pressure (sDBP) between 95 and 119mm Hg recorded manually on the last 2 visits of a single-blind placebo baseline run-in period lasting 3 to 6 weeks prior to the institution of the double-blind study medication. Although the patients enrolled may have been previously treated with antihypertensive agents, the 3- to 6-week placebo period that preceded randomisation to treatment groups was a sufficiently long washout period to preclude any effect of the previous antihypertensive agents. Patients were excluded from enrol-