Br. J. clin. Pharmac. (1993), **35**, 51–54

Evening *vs* morning isradipine sustained release in essential hypertension: a double-blind study with 24 h ambulatory monitoring

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A randomized, double-blind, placebo controlled study evaluated the effects on 24 h ambulatory blood pressure (ABP) of isradipine sustained release (I-SRO) administered once daily, in the morning (AM) or in the evening (PM). Eighteen uncomplicated essential hypertensives (10 men, mean age 55 ± 6 years) with casual sitting DBP 96–110 mm Hg received, according to a triple-way crossover design, I-SRO 5 mg AM, or 5 mg PM, or placebo for 4 weeks. A 24 h ABP monitoring (Spacelabs 90207) was carried out at the end of each treatment. Twenty-four hour BP was 145.3/89.8 mm Hg after randomized placebo. AM and PM I-SRO significantly reduced 24 h BP, by 13.7/8.7 and 12.9/8.2 mm Hg respectively. Daytime (07.00 h–23.00 h) BP significantly decreased by 15.0/9.7 mm Hg with AM and 13.2/8.7 mm Hg with PM regimen; night-time BP (23.00 h–07.00 h) significantly decreased by 11.6/7.1 and 12.3/7.4 mm Hg, respectively. Nocturnal nadir BP values were 132.6/78.1 after randomized placebo, 120.9/71.4 after AM I-SRO and 121.0/72.4 mm Hg after PM I-SRO. Morning peak BP values were 154.6/96.9, 139.5/87.6 and 137.5/85.5 mm Hg, respectively. Mean BP values in the early morning hours (i.e. between 03.00 h and 08.00 h) were significantly decreased by 12.1/7.3 mm Hg after AM and 14.3/7.9 mm Hg after PM intake. No significant differences were detected in the BP lowering effect of the two I-SRO regimens. In hypertensive patients, isradipine sustained release 5 mg once daily given in the morning or in the evening is effective in reducing the 24 h blood pressure profile, irrespective of the time of administration.

Keywords hypertension ambulatory blood pressure monitoring calcium antagonists isradipine

Introduction

Isradipine (PN 200–110, Sandoz Pharma Ltd) is a dihydropiridine calcium channel blocker, which selectively relaxes coronary, cerebral and skeletal muscle vasculature (Hof *et al.*, 1984). It lowers blood pressure by reducing peripheral vascular resistances, with no negative effects on cardiac contractility or atrioventricular conduction (Hof, 1988). Isradipine is an effective antihypertensive drug, when administered 2.5 mg twice daily, as shown by placebo controlled (Man in't Veld *et al.*, 1991) and comparative double-blind studies (Fitscha *et al.*, 1991; Welzel & Burger, 1990). A new, sustained release oral (SRO) formulation of isradipine has been developed, in which hydroxypropylmethylcellulose acts as a gel-forming hydrocolloid, thus prolonging duration of absorption (Mazer *et al.*, 1988). Given once daily, isradipine SRO proved to be as effective as isradipine twice daily in lowering casual blood pressure (Diemont *et al.*, 1991) and mean 24 h ambulatory blood pressure after chronic treatment in essential hypertensives (Diemont *et al.*, 1991; Lacourciere *et al.*, 1990).

As the blood pressure lowering effect of once daily administered drugs might be affected by the time of administration (Nitrendipine Chronopharmacology Study Group, 1990), in this double-blind study we assessed whether isradipine SRO influences 24 h blood pressure profile in a different way when administered in the morning (AM) or in the evening (PM).

Methods

Patients

Eighteen patients (10 men and 8 women; mean (s.d.) age 55 (6) years, range 44–63 years) with uncomplicated

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mild to moderate essential hypertension (casual supine diastolic blood pressure between 96 and 110 mm Hg after a 4-week single-blind placebo run-in) were included in the study. Five of them were previously untreated for hypertension; thirteen were on chronic antihypertensive treatment, on monotherapy (four on β-adrenoceptor blockers, two each on diuretics, calcium channel blockers or ACE-inhibitors) or combination (two on the combination diuretic plus ACE-inhibitor, one on the combination diuretic plus β-adrenoceptor blocker). Any antihypertensive drug was discontinued before starting the placebo run-in, i.e. 4 weeks before randomization. All patients gave their written informed consent to the study.

Protocol of the study

The study was performed according to a double-blind, randomized crossover design. The protocol of the study was approved by an independent Ethics Committee.

Patients were administered, according to a triple way crossover, isradipine SRO 5 mg AM (plus matched placebo PM), or isradipine SRO 5 mg PM (plus matched placebo AM), or matched placebo twice daily, each treatment lasting 4 weeks. Capsules intakes were scheduled at 07.00 h and 19.00 h, respectively. Compliance was checked by capsule counting.

A 24 h non invasive ambulatory blood pressure monitoring was performed at the end of each double-blind treatment, by means of a SpaceLabs 90207 monitor (SpaceLabs Inc., Redmond, WA, USA). The accuracy of this device has been recently determined by the British Hypertension Society Protocol (O'Brien *et al.*, 1991). Monitorings were started in the morning, before 10.00 h; automatic blood pressure measurements were programmed at 15 min intervals throughout the 24 h. Recordings were performed during working days, and the patients were instructed to follow their normal daily activities. Editing was performed according to previously published criteria (Casadei *et al.*, 1988). Systolic blood pressure (SBP), diastolic blood pressure (DBP) and heart rate (HR) mean values were calculated for the 24 h period, the daytime (07.00 h–23.00 h), the night-time (23.00 h–07.00 h) and for twenty-four 1 h subperiods.

Statistical analysis

Statistical analysis was made by using analysis of variance (ANOVA) for a Latin-square design, followed by Student-Newman-Keuls test for comparisons between treatments. P values less than 0.05 were considered as significant. Results are reported as mean (s.e. mean).

Results

Mean casual blood pressure was 163.8 (2.6)/103.8 (1.0) mm Hg after the 4-week placebo run-in period. Mean 24 h, daytime and night-time blood pressure and heart rate values after randomized placebo and isradipine SRO given AM or PM are reported in Table 1.

Mean 24 h blood pressure was 145.3 (3.5)/89.8 (1.5) mm Hg after randomized placebo. Isradipine SRO significantly ($P < 0.01$) reduced mean 24 h blood pressure, by 13.7/8.7 mm Hg after AM and 12.9/8.2 mm Hg after PM administration. Mean daytime blood pressure was significantly ($P < 0.01$) decreased by 15.0/9.7 mm Hg and 13.2/8.7 mm Hg, respectively; mean night-time blood pressure was significantly ($P < 0.01$) decreased by 11.6/7.1 mm Hg and 12.3/7.4 mm Hg, respectively.

Mean hourly blood pressure during the 24 h ambulatory recordings are shown in Figure 1. The antihypertensive effect of isradipine SRO was clearly evident throughout the entire 24 h period, independent of the time of administration: at the end of the 24 h dosing interval (i.e. between 05.00 h and 07.00 h for AM intake; between

Table 1 Twenty-four hour, daytime and night-time blood pressure after 4 weeks of treatment with placebo and isradipine SRO (I-SRO) given in the morning (AM) or in the evening (PM) in 18 hypertensive patients, mean (s.e. mean)

	SBP/DBP (mm Hg)		
	24 h	*Daytime*	*Night-time*
Placebo	145.3 /89.8 (3.5) (1.5)	149.6 /93.7 (3.6) (1.5)	138.1 /83.4 (3.8) (1.7)
I-SRO AM	131.6*/81.1* (2.5) (1.7)	134.6*/83.9* (2.4) (1.8)	126.5*/76.3* (3.1) (1.7)
I-SRO PM	132.4*/81.6* (2.6) (1.9)	136.4*/84.9* (2.7) (2.1)	125.8*/76.0* (2.8) (1.7)

*$P < 0.01$ *vs* placebo.

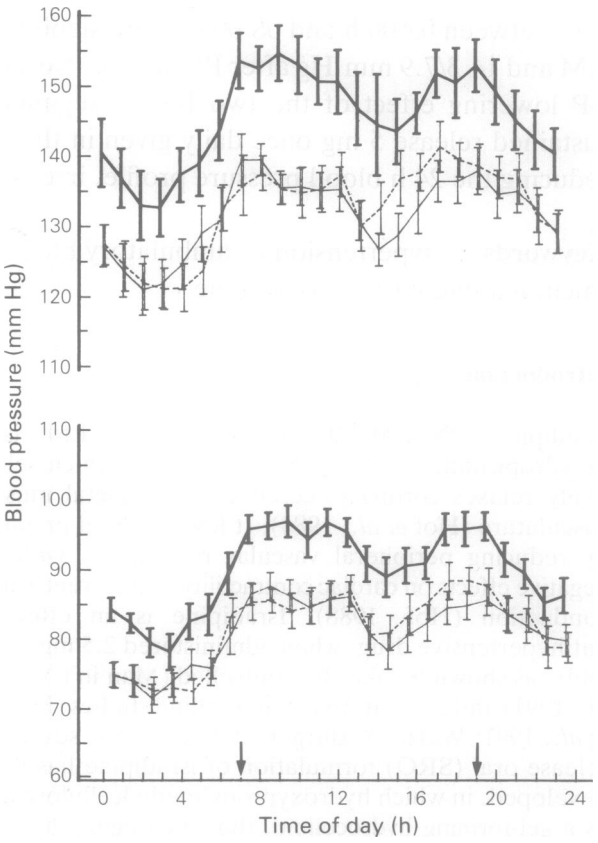

Figure 1 Twenty-four hour blood pressure profile after 4 weeks of treatment with placebo (thick line) and isradipine SRO given in the morning (thin line) or in the evening (dashed line) in 18 hypertensive patients. The vertical bars indicate the standard error and the arrows show the time of drug administration.

17.00 h and 19.00 h for PM intake), blood pressure was significantly lowered by 11.3/8.3 mm Hg ($P < 0.01$) after AM and 10.8/7.3 mm Hg ($P < 0.03$ for SBP and $P < 0.01$ for DBP) after PM intake. Nocturnal nadir mean blood pressure values were 132.6 (4.1)/78.1 (2.6) mm Hg after randomized placebo, 120.9 (3.7)/71.4 (2.1) mm Hg and 121.0 (2.9)/72.4 (1.8) mm Hg after isradipine SRO given AM or PM. Morning peak mean blood pressure values were 154.6 (4.0)/96.9 (2.3), 139.5 (2.3)/87.6 (2.0) and 137.5 (2.5)/85.5 (1.7) mm Hg, respectively.

Mean blood pressure values in the early morning hours (i.e. between 03.00 h and 08.00 h) were significantly ($P < 0.01$) decreased by 12.1/7.3 mm Hg after AM and 14.3/7.9 mm Hg after PM intake.

No significant differences were detected in the blood pressure lowering effect of the two isradipine SRO regimens. Blood pressure variability (average of 24 h standard deviations) decreased from 15.0/11.7 after randomized placebo to 12.5/10.4 and 12.9/10.3, respectively.

The heart rate did not significantly differ from randomized placebo after both AM and PM isradipine SRO. Mean 24 h heart rate values were 71.9 (2.2) beats min^{-1} after randomized placebo, 73.9 (2.0) beats min^{-1} after AM and 72.9 (2.1) beats min^{-1} after PM isradipine SRO. Mean heart rate between 03.00 h and 08.00 h were 66.0 (2.2) beats min^{-1}, 66.1 (1.6) beats min^{-1} and 66.1 (1.8) beats min^{-1}, respectively.

Three patients complained of newly occurring adverse events during the treatment with isradipine SRO: one patient complained of mild headache with both regimens, one of ankle edema during AM administration, one of dizziness during PM administration.

Discussion

The circadian pattern of blood pressure, evaluated both invasively (Millar-Craig *et al.*, 1978) and non-invasively (Degaute *et al.*, 1991), is characterized by a rapid morning rise with a peak around 10.00 h, and a nocturnal falling with a nadir around 03.00 h. In essential uncomplicated hypertension, blood pressure profile maintains its circadian rhythm even if at higher levels than those observed in normotensives (Hany *et al.*, 1987).

The rise of blood pressure with the concomitant heart rate increase that occur in the morning waking hours rapidly increase cardiac workload; this increase, combined with other concomitant physiological events, like augmented sympathetic drive (Panza *et al.*,. 1991), increased platelet aggregability (Tofler *et al.*, 1987) and reduced fibrinolytic potential (Andreotti *et al.*, 1988) may be linked to the observed highest frequency of cardiovascular ischaemic events reported in the early morning hours (Mulcahy *et al.*, 1988; Muller *et al.*, 1985).

Non invasive ambulatory blood pressure monitoring has proved to be useful in evaluating the 24 h blood pressure profile, thus permitting an accurate assessment of the early morning blood pressure rise (Mancia *et al.*, 1988).

This technique is increasingly used in clinical trials for the assessment of the blood pressure lowering effect of antihypertensive drugs (Weber, 1988).

In this study we used non invasive ambulatory blood pressure monitoring to document the extent and duration of the antihypertensive effect of isradipine sustained release given once daily to essential hypertensives for 4 weeks. Several studies have shown that the antihypertensive effect of a given daily dose of isradipine, both in standard (Dahlof, 1989; Leary *et al.*, 1991; Kirkendall, 1988) and SRO formulation (Carretta *et al.*, 1992), is fully displayed within 4 weeks. We compared two drug regimens, i.e. administration in the morning *vs* administration in the evening, to assess whether the time of administration could influence the treatment effects on the 24 h blood pressure profile and particularly on the blood pressure rise in the early morning hours.

As compared with randomized placebo, isradipine SRO once daily satisfactorily reduced ambulatory systolic and diastolic blood pressure throughout the 24 h. During the early morning hours, the blood pressure decreases induced by isradipine SRO were significant and of similar extent after morning and evening administration. No significant differences were detected in the blood pressure lowering effect of the two isradipine SRO regimens. Chronic treatment with isradipine SRO decreased blood pressure without significantly increasing 24 h heart rate values.

In hypertensive patients, isradipine SRO 5 mg once daily given in the morning or in the evening is effective in reducing the 24 h blood pressure profile, irrespective of the time of administration.

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(Received 27 March 1992, accepted 24 July 1992)