Evaluation of Once Daily Endralazine in Hypertension

R. Wu¹, J. D. Spence², and S. G. Carruthers¹

Division of Clinical Pharmacology, Departments of Medicine and Pharmacology¹, University Hospital and
²Victoria Hospital, University of Western Ontario, London, Ontario, Canada

Summary. Endralazine, a novel vasodilator related to hydralazine, exhibits a longer half-life and is only minimally influenced by acetylator status. The antihypertensive action of once daily endralazine has been studied in 17 patients previously controlled with an antihypertensive regimen which included hydralazine and a beta-blocker. Hydralazine was discontinued but other medications were unchanged. Pre-study dosage of hydralazine ranged from 25 mg b.i.d. to 50 mg g.i.d., mean daily dose 126.5 mg. Endralazine was started at a dose of 10 mg o.d. and increased by 10 mg to a maximum of 40 mg o.d. until seated DBP was controlled below 95 mmHg. All 17 patients completed the study. Seated BP significantly decreased from 147.5/99.7 to 133.8/83.9 and standing BP from 145.8/99.2 to 133.6/87.3 mmHg. Ten patients (59%) were successfully controlled with endralazine once daily but 7 patients required twice daily dosage schedules because of lack of BP control at 24 h after dosing or excessive hypotension shortly after dosing. Other adverse effects were headache, palpitations and fatigue. There was a statistically insignificant average weight gain of 1 kg but pedal edema was not observed. Endralazine is an effective antihypertensive agent with adverse symptoms similar to those experienced with hydralazine.

Key words: hypertension, endralazine; once daily therapy, hydralazine, adverse effects

Endralazine (BQ 22-708, Miretilan, Sandoz) is a novel vasodilator related to hydralazine (Lehmann et al. 1977; Lehmann et al. 1978; Reece 1981; Salzmann et al. 1979; Schenker et al. 1979) (Fig. 1). Endralazine has a longer half-life than hydralazine (3.4 h vs 26 min) (Reece 1980 and 1981) and its metabolism, unlike that of hydralazine (Facchini et al. 1981; Reece 1980; Timbrell et al. 1981) is only minimally influenced by acetylator status (Bogers et al. 1983; Holmes et al. 1983; Meredith et al. 1983; Reece et al. 1982)

Endralazine is effective as a twice daily or thrice daily regimen in the treatment of arterial hypertension (Bogers et al. 1983; Donaldson et al. 1983; Dvorak et al. 1984; Elliott et al. 1982; Higgs et al. 1982; Holmes et al. 1983; Kinder et al. 1981; Kirch et al. 1982). Since there is evidence that single daily doses of antihypertensive medications improve compliance (Baird et al. 1984) and since the t½ of endralazine is longer than that of hydralazine, we have investigated the possible efficacy of once daily endralazine in patients previously treated with hydralazine.

Methods

An open dose-ranging study of endralazine was conducted in patients whose seated diastolic blood pressure was controlled at less than 95 mmHg with an an-
A total of 35 patients agreed to participate and completed screening evaluation. Although blood pressures increased in all patients when hydralazine was discontinued, only 17 achieved the entry criterion of seated DBP greater than 95 mmHg. The patients were 12 men and 5 women aged 34-69 years, mean age ± SD of 50.9 ± 9.7 years. Weight ranged from 55.0 to 124.0 kg, mean 87.1 ± 17.7 kg. Pre-study doses of hydralazine ranged from 25 mg b.i.d. to 50 mg q.i.d., mean daily dose 126.5 ± 56.2 mg.

The starting dose of endralazine was 10 mg once daily. Patients were reviewed at intervals of two weeks at which time seated and standing pressures were recorded. If seated DBP exceeded 95 mmHg, endralazine dosage was increased sequentially to 20 mg once daily, 30 mg once daily, or 40 mg once daily maximum dose until the goal pressure of less than 95 mmHg seated was observed on two successive visits to the clinic. Heart rate and weight were recorded at each visit. In addition to a general physical examination, special attention was paid to the examination for pedal edema. If goal DBP less than 95 mmHg was not established or if intolerable adverse effects occurred, a twice daily dosage regimen was substituted to the same maximum daily dosage of 40 mg.

The acetylator status of each patient was assessed following oral sulfadimidine (sulfamethazine) administration using the HPLC method (Whelpton et al. 1981). Seven patients were slow acetylators, 6 fast acetylators and 4 intermediate.

Antinuclear antibody (ANA) was measured at each visit. Patient compliance with therapy was assessed by tablet counts at each visit. Patients were encouraged to record blood pressure at home during the last 2-4 weeks of the study.

Statistical analysis was conducted using Student's t-test for paired data.

Results

All 17 patients completed the study. Ten patients responded to once daily therapy but seven patients required a twice daily regimen because of lack of efficacy at 24 h (n = 6) or post-dosing hypotension (n = 1). The final treatment schedules were as follows: 10 mg o.d. (n = 3), 20 mg o.d. (n = 7), 10 mg b.i.d. (n = 1) and 20 mg b.i.d. (n = 6). The seated sys-