Once-daily Slow-release Hydralazine in Hypertension

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Hydralazine has been used for the treatment of hypertension since 1950 but only since the introduction of β-adrenoceptor-blocking agents has its use again become popular (Koch-Weser, 1976). Originally, hydralazine was given daily in four divided doses but it has been shown to be equally effective and without increased side-effects when given by twice-daily dosage (O'Malley *et al.*, 1975).

The study reported in this paper was designed to compare the antihypertensive effect of a slow-release preparation of hydralazine, given once daily, with the effect of the dose of conventional hydralazine, given daily in two divided doses, in hypertensive patients being treated with a β adrenoceptor blocking agent, slow oxprenolol (Slow Trasicor®).

Twenty-six patients with essential hypertension whose diastolic blood pressure was greater than 90 mmHg entered a double-blind placebo-controlled crossover study in which patients received hydralazine and slow-release hydralazine in random order for 4-week periods. All blood-pressure measurements were taken with a Hawksley random-zero sphygmomanometer by one observer 16–23 h after taking slow-release hydralazine. Compliance was assessed by counting residual tablets and, as different tablets were taken in the morning and evening, it was possible to assess which doses were omitted. Acetylator status was assessed for each patient.

Twenty-one patients completed the study. Three were withdrawn owing to poor

Table 1

Supine arterial blood pressure and heart rate in hypertensive patients receiving hydralazine and slow-release hydralazine in combination with slow-release oxprenolol

	Slow-release oxprenolol (baseline)	Slow-release oxprenolol + Hydralazine	Slow-release oxprenolol + Slow-release hydralazine
Systolic blood pressure (mmHg)	175·6 ± 4·8	149·3 ± 4·6	155·1 ± 4·0
Mean blood pressure (mmHg)	130·4 ± 2·4	111·2 ± 2·8	114·8 ± 2·6
Diastolic blood pressure (mmHg)	107·8 ± 2·0	92·2 ± 2·3	94·7 ± 2·3
Heart rate (beats/min)	68·0 ± 1·8	68·7 ± 1·5	68·4 ± 1·5

Values are means ± s.e. mean; $n = 21$.

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compliance, one owing to accelerated hypertension and one because of gastrointestinal symptoms not attributable to the trial medication.

The mean fall in systolic blood pressure with slow-release hydralazine was 20·5 ± 4·7 mmHg compared with 26·3 ± 5·2 mmHg with conventional hydralazine. The mean fall in diastolic blood pressure was 13·1 ± 2·3 mmHg and 15·6 ± 2·4 with slow-release hydralazine and conventional hydralazine respectively. There was no significant difference in systolic or diastolic blood pressure in patients when taking hydralazine or slow release hydralazine (Table 1). There was no significant difference in heart rate between the two treatment groups.

While compliance was generally good during the study, tablet-counting revealed that 27 evening doses of medication were omitted without a stated reason compared with only nine morning doses ($P < 0·01$).

We conclude that slow-release hydralazine given once-daily is as effective as conventional hydralazine in twice-daily dosage in controlling blood pressure in patients on β-adrenoceptor-blocking agents. The antihypertensive effect of a fixed dose of either compound did not show an obvious association with acetylation phenotype but the numbers studied were small. Finally, patients are more likely to omit the evening dose of medication on a twice-daily dosage regimen, which suggests that once-daily dosage may benefit compliance.

References

Koch-Weser, J. (1976). *New England Journal of Medicine* **295**, 320.

O'Malley, K., Segal, J. L., Israeli, A. H., Boles, M., McNay, J. L. and Dayton, P. G. (1975). *Clinical Pharmacology and Therapeutics* **18**, 581.

J. E. F. Pohl (*Leicester*)

In Dr MacGregor's comparative study of whites and blacks, how does he know that the blacks actually took their propranolol?

G. MacGregor

Propranolol slowed the heart rate in both black and white patients and this finding indicates patient compliance. Furthermore, both groups showed comparable falls in plasma renin activity; and finally we did check the numbers of residual tablets in every case.

J. E. F. Pohl

How do you interpret the results of your experiments on salt and water reinfusion in relation to the blood-pressure-lowering effect of thiazide?

G. MacGregor

I am only suggesting that the loss of sodium and water opposed by the reaction of the renin–angiotensin system to this loss is a major mechanism; it is not the only one, for the blood pressure falls with a diuretic. The unanswered question is how does a loss of sodium and water cause a fall in blood pressure? I am not surprised that acute experiments, such as you refer to, do not completely reverse the changes with diuretics, most of which lower blood pressure over a period of several days.

B. J. Kirby (*Exeter*)

Dr O'Boyle, did you measure blood pressure on any other occasion apart from the clinic attendances? Blood pressure varies during the course of the day and it might not be valid to conclude, on the basis of a couple of isolated readings, that it was controlled over the whole 24 h.

C. O'Boyle

We only measured the blood pressure once in the out-patients clinic and this was between 16 and 23 h after the last dose of slow hydralazine.

D. M. Burley (*Horsham*)

The rationale for producing a slow-release form of hydralazine was partly to extend its duration of activity to cover a 24 h period and partly to diminish side-effects such as headache and flushing, which might occur if a dose greater than 100 mg of conventional hydralazine was given as a single dose. Do your results, Dr O'Boyle, shed any light on this?

C. O'Boyle

There was no significant difference in side-effects between either compound at a similar daily dosage. It would be of interest to study the side-effects of conventional hydralazine given once daily and to assess its duration of activity over a 24 h period. As I said, blood pressure was measured in our patients 16–23 h after the last dose of slow hydralazine: these measurements suggested a reasonable duration of activity, although blood pressure was not actually measured continuously over 24 h.

B. Lewis

Has Dr MacGregor any experience of treating hypertension with a combination of either a vasodilator or a β-blocker with moderate salt restriction?

G. MacGregor

This is of great interest, and an area in which far more properly controlled trials need to be done. We are worried, as others are, about some of the metabolic consequences of diuretics. Moderate salt restriction may be just as effective as a diuretic in many patients. Perhaps in the 1980s we will see a resurgence of interest in salt, not only in treatment but also as a factor in the aetiology of essential hypertension.