DURATION OF EFFECT OF SINGLE DAILY DOSE METHYLDOPA THERAPY

J.M. WRIGHT*, M. OROZCO-GONZALEZ**, G. POLAK† & C.T. DOLLERY

Department of Clinical Pharmacology, Royal Postgraduate Medical School, London W12 0HS

1 Methyldopa has a short plasma half-life, but longer duration of antihypertensive effect. A single bedtime dose of methyldopa has been recommended to improve compliance and decrease side effects.

2 This double-blind crossover study was designed to determine the duration of antihypertensive effect of methyldopa by comparing hourly supine and standing blood pressures, throughout the day during placebo, single morning dose, and single evening dose methyldopa therapy in 10 patients. The major side effects, drowsiness and dry mouth were assessed by visual analogue scale. Exercise blood pressures were measured 6, 12, 18 and 24 h after the dose.

3 The antihypertensive effect of methyldopa peaked after 6–9 h and declined thereafter with a half-life of approximately 10 h. Little antihypertensive effect remained 24–26 h after the dose. The time course of the reduction in blood pressure during exercise and of the major side effects paralleled the antihypertensive effects.

4 The results suggest that the duration of antihypertensive effect of methyldopa is long enough to permit twice daily dosing, but that single daily dosing cannot be recommended for most patients. The study illustrates the importance of knowing the time of the last methyldopa dose when assessing blood pressure measurements in patients taking the drug.

Introduction

In the twenty years since its hypotensive property was first noted (Oates *et al.*, 1960) methyldopa has gained world-wide acceptance as an effective agent in the treatment of hypertension. Methyldopa has a short elimination half-life (Kwan *et al.*, 1976; Stenbeck *et al.*, 1977) and was originally administered three or four times daily. However, the necessity of this inconvenient dosing regimen has been brought into question. The administration of methyldopa once daily at night is now being recommended (Wright *et al.*, 1976; Pipkin *et al.*, 1980) in an attempt to improve compliance (Haynes *et al.*, 1977), and lessen the side effects of drowsiness during the day.

There is evidence suggesting that the antihypertensive effect of methyldopa during chronic therapy is sufficiently long that 3 and 4 times a day dosing is not necessary: (1) When twice daily methyldopa was compared to four times daily methyldopa (14 patients), blood pressure measurements were not

significantly different (Wilson *et al.*, 1979). (2) Single oral doses of methyldopa produced antihypertensive effects which were still noticeable 24 h later (Dollery & Harrington, 1962; Jain *et al.*, 1973). (3) In a double-blind (Wright *et al.*, 1976) and open (Pipkin *et al.*, 1980) cross-over trial, blood pressures were not significantly different after a single bed-time dose of methyldopa, as compared to a multiple daily dose regimen. However, none of those trials permits one to assess the degree of fluctuation in blood pressure that occurs during chronic once daily methyldopa dosing.

The present double blind cross-over trial was designed to directly measure the duration of antihypertensive effect of methyldopa during once daily dosing by comparing blood pressure during placebo therapy with blood pressure during treatment with a single morning and a single evening dose of methyldopa.

Methods

Subjects

Twelve patients between the ages of 30 and 65 years whose blood pressure was adequately controlled on

*Department of Pharmacology, Faculty of Medicine, The University of British Columbia, 2176 Health Sciences Mall, Vancouver, B.C., V6T 1W5, Canada.

**Calle Caurimare, Resid. Atalaya, No. 18; Colinas de Bello Monte, Caracas, 1041, Venezuela.

†Hungarian Institute of Cardiology, P.O.B. 88, 1450 Budapest, Hungary.

methyl dopa with or without added diuretic were selected from the patients attending the Hypertension Clinic at the Hammersmith Hospital, London, U.K. Patients with clinically significant renal, cardiac, or hepatic disease as judged by medical history, physical examination and laboratory studies were excluded from the study. The protocol was approved by the local ethics committee and informed verbal consent was obtained from each patient. The selected patients stopped their methyl dopa medication and were treated for a 2-week period with placebo tablets (identical in appearance and taste to 500 mg methyl dopa tablets) plus or minus diuretic. At the end of this washout period the patients had hourly blood pressures recorded on two consecutive days as described below. The ten patients with diastolic blood pressures greater than 100 mm Hg during this initial study period were entered into the trial.

Design

The trial consisted of three 2-week treatment periods designated treatment I, II, and III, referring to placebo, methyl dopa in a single dose given at 08.30 h, and methyl dopa given in a single dose at 20.30 h, respectively. At the start of each treatment period the patients received two bottles of tablets, one labelled 'Morning dose' (08.30 h) and the other labelled 'Evening dose' (20.30 h). The bottles contained either 112 methyl dopa tablets (500 mg) or 112 indistinguishable placebo tablets. The number of tablets the patients took depended on the desired total daily dose. For example, during the single morning dose period, a patient taking 1 g methyl dopa daily, would be instructed to take two tablets from the morning dose bottle, containing methyl dopa 500 mg tablets, and 2 tablets from the evening dose bottle, containing placebo tablets. The tablets were returned at the end of each treatment and those remaining were counted. Each patient was randomly assigned to one of four orders of treatment: I, II, III; I, III, II; II, III, I; or III, II, I, and they were studied at the end of each treatment period. Neither the patient nor the investigator was aware of the treatment sequence.

The patients were prescribed a total daily dose of methyl dopa which was the nearest multiple of 500 mg to the dosage of methyl dopa which they were previously receiving. Those patients who previously received a diuretic as part of their antihypertensive regimen were instructed to take the same dose of diuretic throughout the trial. All other medications were prohibited for the 6 week duration of the trial.

Study period

At the end of each 2 week treatment period the patients reported to the clinical laboratory at 08.15 h. Blood pressure, pulse and *visual analogue* scores

(described below) were first measured at 08.30 h and were repeated at hourly intervals throughout the day until 22.30 h. After the last measurements at 22.30 h the patients went home and returned the next morning at 08.30 h. On this second day measurements were made at 08.30, 09.30 and 10.30 h only. Blood pressure and pulse rate during submaximal exercise were measured at 14.30 and 20.30 h the first day and at 08.30 h the second day. During the first study day the patients took their medications at 08.30 and 20.30 h as they had for the previous two weeks, but on the second study day the first dose of the next treatment period was not taken until 11.00 h.

Measurements

Blood pressure (average of 3 determinations at 1 min intervals) was measured by a Roche arteriosonde after 10 min in the supine position and again after 5 min in the erect position. Supine and erect pulse rate was counted for 30 s by palpation at the wrist.

After the recumbent blood pressure and pulse rate were recorded, the patients were asked to mark two 10 cm lines (visual analogue scales). One scale, for a sedative score, was labelled 'wide awake' at one end and 'as sleepy as you have been' at the other end. The other scale, for dry mouth score, was labelled 'mouth, moist (normal)' at one end and 'mouth, as dry as it can be' at the other end.

On 3 occasions (14.30 h and 20.30 h the first day and 08.30 h the second day), submaximal exercise was performed on a bicycle ergometer at a load previously standardized to achieve a heart rate of about 150 beats/min after 5 min exercise. Heart rate was recorded during the last 30 s of exercise by ECG. Blood pressure was recorded in duplicate with a Hawksley random zero sphygmomanometer during the fifth minute of exercise.

At the end of each treatment period the patients were asked if they experienced any adverse or unusual signs or symptoms during the previous 2 weeks. Side effects thus elicited were recorded and rated as mild, moderate, or severe.

Statistical analysis

The data was analysed by 3-way analysis of variance. Where appropriate, paired *t*-tests were used to compare means. Regression analysis was performed by standard methods.

Results

The clinical details of the 10 patients who started and completed the trial are summarized in Table 1. Tablet counts revealed that only 2 doses of active drug, one dose in each of 2 patients, were returned out of a total

Table 1 Patient data

Patient	Sex	Age (years)	Weight (kg)	Height (cm)	Methyldopa daily dose (g)	Bendroflumazide daily dose (mg)
1	M	57	75	170	1.5	10
2	F	49	52	152	2.0	
3	M	58	87	166	4.0	10
4	F	63	69	160	1.0	5
5	F	64	55	150	0.5	5
6	F	58	65	168	1.0	5
7	F	51	76	162	1.0	
8	M	37	79	179	0.5	
9	M	55	72	179	1.0	5
10	M	46	54	154	1.0	

of 280 methyldopa doses, suggesting excellent compliance.

Supine and standing blood pressures during the two treatment periods were significantly lower ($P < 0.001$) than during the placebo period (Figures 1 and 2). The methyldopa effect is most striking after the morning dose; the peak reduction in blood pressure occurs 6–9 h after the dose, and the antihypertensive effect is small 0–2 h and 24–26 h after the dose. With the evening dose, blood pressure is lowest in the early morning and approaches placebo values by 24 h after the dose.

After the peak antihypertensive effect of methyldopa, the blood pressure gradually increases. We have calculated the rate of this rise in blood pressure (decline of pharmacological effect) by expressing the lying and standing systolic and diastolic blood pressures as a percentage change from the same measurements while receiving placebo, and plotting the regression of the mean log percent change against time. Each of the regression lines so calculated was highly significant ($P < 0.001$); the half-lives of the antihypertensive effect calculated from these lines are 10.3; 10.1, 9.1 and 9.3 h for the lying systolic and diastolic, and standing systolic and diastolic blood pressures, respectively. The data and calculated line for standing systolic blood pressure is shown in Figure 3.

The postural effect of methyldopa was analysed by comparing the lying minus the standing systolic and diastolic pressures during placebo with the same measurement during the methyldopa treatment periods. Methyldopa produced a small, but significant ($P < 0.01$, 3-way ANOVA) postural drop in blood pressure as compared to placebo. The overall, mean $\pm$ s.e. mean systolic postural drop was 7.0 ± 1.0 , 4.4 ± 0.4 and 0.3 ± 0.5 mm Hg on morning methyldopa, evening methyldopa and placebo, respectively; the overall mean diastolic drop was -3.3 ± 0.6 , -5.4 ± 0.7 , and -8.4 ± 0.5 mm Hg. A negative

value indicates a rise in the measured pressure on standing. The maximum postural effect occurred 8 to 15 h after the dose of methyldopa.

Heart rates were also significantly lower ($P < 0.01$) during both methyldopa treatment periods. The overall mean $\pm$ s.e. mean supine heart rate on morning methyldopa, evening methyldopa and placebo was 67.7 ± 0.8 , 69.1 ± 0.6 and 75.3 ± 0.8 beats/min, respectively; the overall mean standing heart rate was 78.5 ± 0.9 , 79.4 ± 0.8 and 87.7 ± 1.0 beats/min, respectively.

Exercise blood pressures and heart rates were measured 6, 12, and 24 h after the morning dose and 12, 18, and 24 h after the evening dose. The magnitude and time course of the effect of methyldopa on these parameters (Figure 4) is similar to those at rest.

Adverse symptoms volunteered by the patients during the trial were judged to be mild to moderate. During morning methyldopa treatment, 5 patients complained of drowsiness in the afternoon, and 4 patients complained of dry mouth. During evening methyldopa treatment, three patients complained of insomnia and fitful sleep; other patients complained of morning symptoms, two with drowsiness, one with dry mouth and one with orthostatic faintness.

The two commonest side effects of methyldopa, drowsiness and dry mouth, were assessed hourly using visual analogue scales. These data, plotted as the mean difference from placebo, are shown in Figure 5.

Discussion

This study demonstrates the time course of antihypertensive effect of methyldopa during chronic once daily oral dosing. The peak effect is delayed and occurs 6–9 h after the dose; the effect then declines with a half-life of approximately 10 h and only a small effect remains by 24–26 h. This time course is similar

Figure 1 The effect of a single morning (a) and evening (b) dose of methyldopa (□) as compared to placebo (■) on supine systolic and diastolic blood pressure (mean $\pm$ s.e. mean) in 10 hypertensive patients. Methyldopa was administered at 08.30 or 20.30 h (see arrows) and the time of the blood pressure measurements are indicated as hours after the dose. Blood pressures were measured hourly from 08.30 until 22.30 h the first day and from 08.30 to 10.30 h the second day. The difference of individual means from placebo (by paired *t*-test) is indicated with asterisks (**P* < 0.05, ***P* < 0.01).

to that found in earlier studies where the antihypertensive effect was measured after a single oral dose (Dollery & Harrington, 1962; Gillespie *et al.*, 1962). The time course of antihypertensive effect does not correlate with the rapid serum half-life of methyldopa (1–2 h); however, it may correlate with a second phase serum half-life of methyldopa and/or metabolites (Stenbeak *et al.*, 1977). This second phase half-life may reflect methyldopa metabolites leaving the site of action in the brain.

The marked fluctuation in blood pressure seen in this study after a single morning dose of methyldopa emphasizes the importance for the physician to consider the time the drug was ingested when evaluating a blood pressure measurement. This effect would be expected to be less marked with more frequent dosing regimens, but it probably contributes to the variation in blood pressure commonly seen in clinical practice.

The degree of fluctuation in blood pressure observed would not have been predicted from earlier studies comparing once daily bedtime doses of methyldopa with multiple daily dose therapy (Wright *et al.*, 1976; Pipkin *et al.*, 1980). Two major disadvantages are associated with studies of that type. Most importantly, blood pressure may not be measured at times of maximal (6–9 h) and minimal (0–2 h) drug effect. In the previous studies of once daily methyldopa, blood pressures were not measured at these times. Secondly, compliance and oral bioavailability for once daily regimen tablets may be greater than for multiple daily regimen tablets, causing a bias towards lower blood pressure during the once daily regimen.

Blood pressures on placebo tended to be lower in the mid-afternoon as compared to the morning and evening. This pattern is somewhat different from that

Figure 2 The effect of a single morning (a) and evening (b) dose of methyldopa (□) as compared to placebo (■) on standing systolic and diastolic blood pressure (mean $\pm$ s.e. mean) in 10 hypertensive patients. Methyldopa was administered at 08.30 or 20.30 h (see arrows) and the time of the blood pressure measurements are indicated as hours after the dose. Blood pressures were measured hourly from 08.30 until 22.30 h the first day and from 08.30 to 10.30 h the second day. The difference of individual means from placebo (by paired *t*-test) is indicated with asterisks (* P < 0.05, ** P < 0.01).

seen with continuous intra-arterial monitoring where a steady decline in blood pressure was seen throughout the waking hours (Millar-Craig *et al.*, 1978).

Methyldopa given once daily in this study even in a dose as high as 4 g was well tolerated and all patients completed the trial. However, it should be noted that these patients were selected because methyldopa had proved to be effective and well tolerated. Drowsiness during the day was experienced more frequently with the morning dose; insomnia and fitful sleep were more frequent with the evening dose. Interference with sleep in patients taking methyldopa may occur more commonly than is recognized; Baekeland & Lundwall (1971) demonstrated that methyldopa made sleep latency more variable, increased rapid

eye movement sleep, and decreased stage 4 sleep during the first 3 h of sleep.

The visual analogue scale proved to be very sensitive in detecting drowsiness and dry mouth. As would be expected for a centrally-acting antihypertensive agent, the time course of these central side effects paralleled the antihypertensive effect.

The effect of the fluctuation in blood pressure with once daily methyldopa on long-term morbidity and mortality is unknown. The Veterans Administration Cooperative Study (1970), documenting a reduction in morbidity and mortality with control of hypertension, utilized the long-acting drugs hydrochlorothiazide and reserpine, or hydralazine, and the drugs were given in divided daily doses. Therefore, it is

Figure 3 The logarithmic decline of methyldopa antihypertensive effect from the peak effect over time in 10 patients receiving methyldopa as a single morning (●) and evening (○) dose. Each dot represents the mean % decrease from placebo in standing diastolic blood pressure for 10 patients at the time indicated. The straight line ($y = -\log 1.1x + \log 30.6$) was calculated by regression analysis ($r = 0.86$; $P < 0.001$) and represents a half-life of antihypertensive effect of 9.1 h.

Figure 4 The effect of placebo (□), single morning (▨), and single evening (▤) dose methyldopa on mean $\pm$ s.e. mean blood pressure (BP) and pulse rate during submaximal exercise on a bicycle ergometer. The time of day the measurements were recorded is indicated at the bottom and the hours after receiving methyldopa is indicated below the bars. The difference of individual means from placebo (by paired t -test) is indicated with asterisks (* $P < 0.05$, ** $P < 0.01$).

Figure 5 Effect of single morning dose (●) and single evening dose (○) methyldopa on mean sedative (a) and dry mouth (b) score. Scores were measured by visual analogue scale (100 mm) and the values shown represent the mean score on drug minus score on placebo; s.e. bars are omitted for clarity. Morning and evening dose data are plotted on the same graph. The difference of individual means from zero (by paired *t*-test) is indicated with asterisks (* $P < 0.05$, ** $P < 0.01$).

reasonable to attempt to achieve sustained lowering of blood pressure in our patients. Single bedtime dosing of methyldopa is associated with less fluctuation in daytime blood pressures than single morning dosing, but blood pressure control late the following day is unsatisfactory, and the effect of bedtime methyldopa on sleeping blood pressure has not been studied. The documented duration of antihypertensive action of methyldopa in this study suggests that

twice daily dosing would be satisfactory; however, for the reasons indicated, single daily dose methyldopa cannot be recommended for most patients.

We thank Mrs Julia Daniel for the excellent clinical assistance, and Merck, Sharp and Dohme Research Laboratories for financial assistance. J.M.W. was supported by a Canadian Medical Research Council Fellowship.

References

- BAEKLAND, F. & LUNDWALL, L. (1971). Effects of methyldopa on sleep patterns in man. *Electroencephalogr. clin. Neurophysiol.*, **31**, 269–273.
- DOLLERY, C.T. & HARRINGTON, M. (1962). Methyldopa in hypertension. Clinical and pharmacological studies. *Lancet*, **i**, 759–763.
- GILLESPIE, L., OATES, J.A., CROAT, J.R. & SJOERDSMA, A. (1962). Clinical and chemical studies with methyldopa in patients with hypertension. *Circulation*, **25**, 281–291.
- HAYNES, R.B., SACKETT, D.L., TAYLOR, D.W., ROBERTS, R.S. & JOHNSON, A.L. (1977). Manipulation of the therapeutic regimen to improve compliance: conceptions and misconceptions. *Clin. Pharmac. Ther.*, **22**, 125–130.
- JAIN, A.K., RYAN, J.R., McMAHON, F.G. (1973). The effect of single morning doses of alphamethyldopa on blood pressure. *Clin. Pharmac. Ther.*, **14**, 137–138.
- KWAN, K.C., FOLTZ, E.L., BREAU, G.O., BAER, J.E. & TOTARO, J.A. (1976). Pharmacokinetics of methyldopa in man. *J. Pharmac. exp. Ther.*, **198**, 264–277.
- MILLAR-CRAIG, M.W., BISHOP, C.N. & RAFTERY, E.B. (1978). Circadian variation of blood pressure. *Lancet*, **i**, 795–797.
- OATES, J.A., GILLESPIE, L., UDENFRIEND, S. & SJOERDSMA, A. (1960). Decarboxylase inhibition and

- blood pressure reduction by α -methyl-3,4-dihydroxy-DL-phenylalanine. *Science*, **131**, 1890-1891.
- PIPKIN, M.E., JOHNSTON, P.E., MILLER, S.T. & SELP, T.H. (1980). Single daily dosing of methyldopa. *Curr. Ther. Res.*, **28**, 335-339.
- STENBEAK, O., MYHRE, E., RUGSTAD, H.E., ARNOLD, E. & HANSEN, T. (1977). Pharmacokinetics of methyldopa in healthy man. *Eur. J. clin. Pharmac.*, **12**, 117-123.
- VETERANS ADMINISTRATION COOPERATIVE STUDY GROUP ON ANTIHYPERTENSIVE AGENTS (1970). Effects of treatment on morbidity in hypertension. II. Results in patients with diastolic blood pressure averaging 90 through 114 mm Hg. *J. Am. med. Ass.*, **213**, 1143-1152.
- WILSON, L., ROBERTS, A. & O'HALLORAN, M. (1979). Twice daily methyldopa: home blood pressure recordings. *Med. J. Aust.*, **2**, 363-364.
- WRIGHT, J.M., McLEOD, P.J. & McCULLOUGH, W. (1976). Antihypertensive efficacy of a single bedtime dose of methyldopa. *Clin. Pharmac. Ther.*, **20**, 733-737.

(Received October 20, 1981)