The Use of Methyldopa in the Elderly

L.E. RAMSAY, MB, MRCP(UK)
Consultant Physician and Associate in Medicine,
University Department of Therapeutics, Royal Hallamshire Hospital, Sheffield

Following the introduction of β-blockers, the role of methyldopa in the management of hypertension changed considerably. Formerly a drug of first choice, it is now used less widely because of its subjective adverse effects, but retains a useful place in two particular situations: as a second drug (added to a thiazide diuretic) in patients with a contraindication to β-blockade; and as third or fourth choice when diuretic, β-blocker and possibly a vasodilator fail to control the blood pressure. One consequence of this altered role is the relatively frequent use of methyldopa in elderly patients, because they are more likely to have some contraindication to β-blockade. In fact, it is often recommended that methyldopa should be avoided in the elderly, although the reason for this is not clear [1, 2]. The question is important, because almost half the patients undergoing treatment for hypertension in Britain are 65 or older[3]. I have surveyed the use of methyldopa in ordinary clinic conditions, examining the pattern of prescribing in relation to age, and comparing the outcome of treatment in the elderly with that in younger patients in regard to the hypotensive effect, orthostatic action and adverse effects.

There has been concern about elderly hypertensive patients developing disabling symptoms[4], strokes[5, 6] or myocardial infarction[7] when their blood pressure is lowered. A further aim of this study was to examine the relationship, if any, between vascular complications in the elderly and changes in blood pressure during treatment with methyldopa, and specifically, whether vascular accidents were related to too much or too little antihypertensive treatment.

Methods

The records of all 63 patients starting methyldopa in the Sheffield hypertension clinic during the 15 months October 1978—December 1979 were examined retrospectively. Data were extracted by a research nurse who was unaware of the purpose of the study. Results were recorded up to the first visit after six months of taking methyldopa, or until the drug was stopped. Follow-up was less than six months in 17 patients (27 per cent), but their age distribution was such that the results were not biased. Blood pressure was measured on the right arm at routine visits using a standard mercury sphygmomanometer, taking phase 5 (disappearance) diastolic pressure. The measurements are open to digit preference, observer bias and observer variation, but these errors would not bias the present analysis. The statistical methods were the Mann-Whitney U test, Pearson's r, chi-square with Yates' correction, the median test and Fisher's exact test[8].

Results

Patients

When methyldopa was started, the 63 patients, who were taking on average 2.2 anti-hypertensive drugs, had a mean blood pressure of 202/109 mm Hg lying down. The blood pressure at the previous visit was similar (196/109 mm Hg), so that subsequent changes cannot be ascribed to regression to the mean. Methyldopa was added to the existing treatment in 41 patients and replaced another drug in 22. Of the 63 patients 24 (38 per cent) were aged 65 years or more (range 65-79, mean 70.6 years). This figure of 38 per cent elderly was slightly higher than that for all patients attending the hypertension clinic (30 per cent elderly), and much higher than that for consecutive patients starting hydralazine during the same period (17 per cent elderly). The younger patients were divided into two groups; those up to 56 years (range 32-55, mean 49.4, n = 19) and those aged 56-64 (mean 60.0, n = 20). Features of the three age groups are shown in Table 1. Systolic blood pressure was significantly higher in the elderly group than in the younger groups, while diastolic pressures were similar in the three groups. With increasing age the proportion of women increased, body-weight fell, serum creatinine was higher, and more patients had complications of hypertension.

Methyldopa Treatment

The pattern of prescribing differed with age (Table 2). In the elderly methyldopa was used only as a second drug (after diuretic, 46 per cent) or third drug (usually after diuretic and β-blocker, 54 per cent), whereas it was used as the fourth drug (usually after diuretic—β-blocker—vasodilator) in 28 per cent of the younger patients. The reason for the earlier use of methyldopa in older patients was the frequent presence of contraindications to β-blockers, particularly cardiac failure. Only 42 per cent of the elderly were taking a β-blocker compared with 67 per cent of younger patients (P<0.1). The starting dose of methyldopa was 125 mg b.d. in 37 patients, 250 mg b.d.,
in 23, and higher in 3. The final dose exceeded 500 mg b.d. in only 7 patients.Dosage differed little with age (Table 2).

**Hypotensive Response**

Changes in recumbent blood pressure were expressed as a percentage fall, to allow for the initial blood pressure differences between the groups. At the first visit after methyldopa was added, the response differed little with age, but by the third visit the response was considerably larger in the elderly than in the young (systolic fall 21.6 per cent v. 11.7 per cent, P < 0.05; diastolic fall 16.5 per cent v. 9.4 per cent, P < 0.01; Fig. 1) although the dose of methyldopa and duration of treatment were similar in these groups. Patients aged 56-64 years had an intermediate response (14.6 per cent/12.4 per cent) but were less well matched as regards the dose and duration of methyldopa treatment.

**Orthostatic Effect**

Patients taking sympathetic blocking drugs other than β-blockers were excluded from this analysis. Before methyldopa was added, the elderly showed an orthostatic blood pressure change of −13.6/−5.9 mm Hg, compared to −7.3/+5.1 mm Hg in the young. The difference in diastolic change was significant (P < 0.02), and there was a correlation between age and the diastolic change on standing (r = −0.43, P < 0.02; Fig. 2), but not the systolic change (r = −0.10). During treatment with methyldopa 500 mg daily the additional orthostatic effect was similar in the elderly (−11.8/−3.2 mm Hg) and the

---

**Table 1.** Mean (and range) data for patients at the visit when methyldopa was started, related to age.

|                        | 32-55 years  | 56-64 years  | 65-79 years |
|------------------------|--------------|--------------|-------------|
|                        | (n = 19)     | (n = 20)     | (n = 24)    |
| Sex (M:F)              | 11:8         | 13:7         | 8:16        |
| Age (years)            | 49.4         | 60.0         | 70.6        |
| Weight (kg)            | 73.8 (55-100)| 70.4 (54-96) | 66.7 (44-85)|
| BP (mm Hg): systolic   | 188 (140-234)| 199 (158-245)| 215 (152-290)*|
|                        | 108 (80-126) | 106 (88-125) | 111 (60-135)|
| BP (mm Hg): diastolic  | 118 (74-201) | 115 (80-258) | 137 (74-328)|
| Serum creatinine (μmol/litre) | 0        | 7            | 8           |
| Cardiac failure        | 4            | 7            | 3           |
| Angina/myocardial infarct | 1        | 2            | 3           |
| Previous stroke        |              |              |             |

*P < 0.02 versus those aged 32-55 years

**Table 2.** Details of methyldopa prescribing related to age.

|                        | 32-55 years  | 56-64 years  | 65-79 years |
|------------------------|--------------|--------------|-------------|
|                        | (n = 19)     | (n = 20)     | (n = 24)    |
| Methyldopa used as:*   |              |              |             |
| second drug            | 7            | 5            | 11          |
| third drug             | 6            | 10           | 13          |
| fourth drug            | 6            | 5            | 0           |
| Initial dose (mg/day)  | 408 (250-1500)| 369 (250-750)| 348 (250-750)|
| Highest dose (mg/day)  | 855 (250-2000)| 631 (250-2000)| 707 (250-2000)|
| Duration follow-up (weeks) | 25.3    | 25.1         | 21.9        |

*Distribution in elderly differed from that in patients aged 32-64 years; χ^2 = 8.25, P < 0.02.

---

**Fig. 1.** Percentage fall in blood pressure at the three clinic visits after methyldopa was started, at visit 0, for those aged 32-55 years (○ − − − ○, n = , follow-up 15th week, dose methyldopa 775 mg/day); 56-64 years (□ − − − □, n = 15, 19th week, 600 mg/day); and 65-79 years (← , n = 15, 15th week, 783 mg/day). Methyldopa replaced another drug in 8/15 young, 3/15 aged 56-64 years, and 6/15 elderly patients.
Adverse effects leading to withdrawal of methyldopa showed some relationship to the initial dose. Only 16 per cent of those who started at 125 mg b.d. stopped, whereas 40 per cent of those starting at a higher dose had to discontinue the drug ($\chi^2 = 3.25, P<0.1$).

**Vascular Complications in the Elderly**

Six of the elderly patients (25 per cent) had vascular complications within seven weeks (range 4 days to 30 weeks) of starting methyldopa.

**Patient 1**, a 69-year-old man with cardiac and renal failure, died four days after methyldopa was substituted for acebutolol. His death could be explained by his poor cardiovascular state, or by β-blocker withdrawal.

**Patients 2-6** were admitted to hospital on average 17 weeks (range 13-30 weeks) after starting methyldopa, four with strokes and one with acute coronary insufficiency. At the time of starting methyldopa these patients did not differ significantly from those who remained free of complications (Table 4). They had attended the clinic on average six weeks before admission and this was on average 11 weeks after starting methyldopa. Data for that clinic visit were compared with those at the visit nearest to 11 weeks for each of the patients without complications (Table 5). Patients destined to have a vascular complication had no response to methyldopa, with mean blood pressures of 194/112 mm Hg initially, 187/111 mm Hg after 11 weeks of methyldopa treatment, and 193/117 mm Hg when admitted. In contrast, those who remained without complications had large falls in blood pressure, from 224/111 mm Hg initially to 182/94 mm Hg at 11 weeks, and 174/91 mm Hg after 22 weeks. The fall in mean arterial pressure after 11 weeks was significantly less for those who developed complications (Table 5). No patient with a diastolic pressure below 100 mm Hg after 11 weeks (mean 168/85 lying, 156/85 standing, n = 11) developed any vascular complication, whereas five of 11 with higher diastolic pressures (mean 198/110 mm Hg lying, 173/103 mm Hg standing) developed complications ($P = 0.018$, median test). Similarly, none of 11 patients with falls in diastolic pressure greater than 10 per cent (mean 22 per cent) had a complication, compared with five of 11 patients with smaller falls in diastolic pressure (mean 0 per cent, $P = 0.018$).

### Table 3. Adverse effects recorded in the 6 months after methyldopa was started, related to age.

|                        | 32-55 years | 56-64 years | 65-79 years |
|------------------------|-------------|-------------|-------------|
| No adverse effects     | 5 (26%)     | 8 (40%)     | 10 (43%)    |
| Mild adverse effects   | 7 (37%)     | 6 (30%)     | 4 (17%)     |
| Dose reduced           | 3 (16%)     | 0 (0%)      | 3 (13%)     |
| Methyldopa stopped     | 4 (21%)     | 6 (30%)     | 6 (26%)     |
| Adverse effects/patient| 1.42        | 0.95        | 0.74        |
| Dose at first adverse effect (mg) | 571 | 552 | 731 |
| Tired/drowsy            | 10 (53%)*   | 5 (25%)     | 5 (22%)     |
| Dizziness              | 3 (16%)     | 5 (25%)     | 4 (17%)     |

* $\chi^2 = 3.95, P<0.05$ versus patients aged 56-79 years.
Table 4. Mean (and range) of values at the time of starting methyldopa for elderly patients who subsequently had vascular complications, and those who developed no complication.

| Vascular complication | No complication |
|-----------------------|-----------------|
| (n = 5)               | (n = 17)        |
| Age (years)           | 71.8 (67-76)    | 69.9 (65-79) |
| Sex (M:F)             | 1.5:1           | 2.4:1         |
| Weight (kg)           | 66.4 (54-77)    | 66.2 (44-83)  |
| Vascular disease*     | 60%             | 41%           |
| Serum creatinine > 150 μmol/litre | 20% | 18% |
| Systolic BP (mm Hg)†  | 194 (180-220)   | 224 (164-290) |
| Diastolic BP (mm Hg)  | 112 (110-120)   | 111 (60-135)  |
| Mean no. of drugs     | 1.8             | 1.9           |
| No. of drugs stopped  | 0.2             | 0.3           |

*Previous stroke, ischaemic heart disease, peripheral vascular disease.
†Difference approached significance (P<0.1).

Table 5. Mean (and range) of values at the visit approximately 11 weeks after starting methyldopa for patients who subsequently had vascular complications, and those who developed no complications.

| Vascular complication | No complication |
|-----------------------|-----------------|
| (n = 5)               | (n = 17)        |
| Duration follow-up (weeks) | 10.8 | 10.2 |
| Dose methyldopa (mg/day) | 750 (250-2000) | 588 (250-2000) |
| Systolic BP (mm Hg)    | 187 (128-240)   | 182 (130-228)  |
| Diastolic BP (mm Hg)   | 111 (100-128)   | 94 (66-126)    |
| Fall in systolic BP (mm Hg)‡ | 6.8 | 42.5 |
| Fall in diastolic BP (mm Hg)§ | 1.2 | 17.1 |
| Fall in mean pressure (mm Hg)† | 3.1 | 25.6 |
| Postural BP change (mm Hg) | - 32/-6 | - 17/-3 |

‡P<0.1.
§P<0.05 for difference between groups.

Discussion

Jackson et al.[4] described five elderly patients admitted to hospital with severe hypotension within one week of starting methyldopa 750 mg daily, but the only formal study of the subject[9] showed that older patients were significantly less likely to develop hypotension as an adverse reaction to methyldopa. The present survey does not suggest that methyldopa causes special problems in the elderly. The initial response was similar at all ages, and catastrophic falls of blood pressure were not seen in the older patients. After three to four months of treatment the elderly showed significantly larger responses to methyldopa than the young. The orthostatic effect of methyldopa itself was not larger in the elderly, nor were complaints of dizziness more common. Adverse effects, particularly tiredness or drowsiness, were less frequent with increasing age and also appeared first at a higher daily dose. There is evidence that the elderly are generally less likely to consider themselves sleepy or depressed, and are an uncomplaining group[10]. Nevertheless, adverse effects troublesome enough to cause withdrawal of methyldopa were as common in the elderly as in the young.

Elderly patients are thought to be at particular risk from postural hypotension, because ageing is associated with reduced baroreflex sensitivity[11], but, surprisingly, a correlation between age and orthostatic blood pressure change has not been reported. In this study there was a weak but significant correlation between age and the postural fall in diastolic blood pressure, both before and during methyldopa treatment. These patients were already on treatment before methyldopa was started, but not with drugs that usually cause orthostatic falls in blood pressure. This correlation may not be due to age per se, as orthostatic hypotension is related to the severity of hypertension and vascular disease[12, 13] and the elderly patients in this study clearly had more severe hypertension (see Table 1).

One quarter of the elderly patients had vascular complications during follow-up and the question arises whether they were caused by the hypertension itself, or by over-vigorous treatment causing 'poor perfusion' strokes[5, 6] or coronary occlusion[7]. In this group of patients the answer was clear. Those who developed complications had no hypotensive response to methyldopa, so that complications occurred in a setting of persistent hypertension. There were no untoward consequences in those patients who had large falls in blood pressure. 'Poor perfusion' strokes undoubtedly occur, but they are a pathological curiosity[5], whereas Kennedy and Hoffbrand[14] could collect 20 'uncontrolled hypertension' strokes from one hospital in eight months and more than half were elderly. Careful reviews of all the evidence concerning treatment of hypertension in the
elderly suggest that the risks of lowering blood pressure have been exaggerated, while the potential benefits have been ignored[1, 2]. The results of the present study support this view. However, the patients studied had severe sustained hypertension, and the balance of risk and benefit may be different in elderly patients with mild uncomplicated hypertension.

In summary, methyldopa was never used as a drug of first choice in this clinic, but it often had to be prescribed for elderly patients with severe hypertension because of contraindications to β-blockade, particularly cardiac failure. As in other studies[15], adverse effects were very common, with a quarter of the patients stopping the drug within six months regardless of age, but methyldopa was at least as acceptable to the elderly as to the young. The chance of the drug being tolerated was improved by starting with a dose no higher than 125 mg b.d.

Acknowledgement

I am greatly indebted to Mrs Lynne Latham who extracted the data used in this study.

References

1. Koch-Weser, J. (1979) In Drugs and the Elderly, pp. 247-262. (ed J. Crooks and I. H. Stevenson.) London: Macmillan.
2. O'Malley, K. and O'Brien, E. (1980) New England Journal of Medicine, 302, 1397.
3. Tudor Hart, J. (1980) Journal of the Royal College of General Practitioners, Occasional paper 12, pp. 11-12.
4. Jackson, G., Piercianowski, T. A., Mahon, W. and Condon, J. (1976) Lancet, 2, 1317.
5. Graham, D. I. (1975) British Medical Journal, 2, 739.
6. Jones, J. V. and Graham, D. I. (1978) American Heart Journal, 96, 270.
7. Stewart, I. McD. G. (1979) Lancet, 1, 861.
8. Siegel, S. (1956) Nonparametric statistics for the behavioural sciences. London: McGraw-Hill.
9. Lawson, D. H., Gloss, D. and Jick, H. (1978) American Heart Journal, 96, 572.
10. Bulpitt, C. J., Dollery, C. T. and Carne, S. (1974) Journal of Chronic Disease, 27, 309.
11. Gribbin, B., Pickering, T. G., Sleight, P. and Petro, R. (1971) Circulation Research, 29, 424.
12. Frohlich, E. D., Tarazi, R. C., Utruy, M., Duscan, H. P. and Page, I. H. (1967) Circulation, 36, 387.
13. Molchan, M., Dissmann, Th., Halim, S., Loehmann, F. W. and Oelkers, W. (1972) Clinical Science, 42, 209.
14. Kennedy, P. G. E. and Hoffbrand, B. I. (1978) British Medical Journal, 2, 1605.
15. Editorial (1975) British Medical Journal, 1, 646.

Bobby Hutch's Choice

'Doctors have at all times incurred the abuse of the laity, but they have also received almost extravagant praise; censure and praise being alike often ill-deserved.' So wrote Sir Robert Hutchison (Bobby Hutch to a past generation of Old Londoners) and Dr Wauchope in their collection of quotations published in 1955. Almost fifty years later some of these quotations must have a new flavour for the reader. The current problems of inner city practice are surprisingly illuminated by the great Dr Johnson. 'A physician in a great city seems to be the mere plaything of fortune; his degree of reputation is, for the most part, totally casual; they that employ him know not his excellence; they that reject him know not his deficiency.' Of course the context of the original writing or speech makes all the difference. Would Gladstone have been so laudatory if he had not been giving an address at Guy's? '... I congratulate the profession in its independence. It does not rely on endowment, but on its own exertions directed to meeting human wants. There is no great profession which has so little to say to the public purse, and which so moderately and modestly dips its hand into that purse.' If only he had known the shape of things to come. Contrast this with Lloyd George's dictum 'While I was dealing with the Insurance Act I had much to do with doctors. I found them unreasonable and unruly.'

Perhaps the most dated quotation comes from Rudyard Kipling's address to the students of the Middlesex Hospital in 1908. It is redolent of duty and Empire. 'Every sane human being is agreed that this long-drawn fight for time, which we call Life, is one of the most important things in the world. It follows therefore that you, who control and oversee this fight, and you who will reinforce it, must be among the most important people in the world. Certainly the world will treat you on that basis. It has long ago decided that you have no working hours that anybody is bound to respect, and nothing but extreme bodily illness will excise you in its eyes from refusing to help a man who thinks he may need your help at any hour of the day or night. Nobody will care whether you are in your bed or in your bath, on your holiday or at the theatre... In all times of flood, fire, famine, plague, pestilence, battle, murder, and sudden death, it will be required of you that you report for duty at once, go on duty at once, and remain on duty until your strength fails or your conscience relieves you, whichever may be the longer period... May I remind you of some of your privileges? You and kings are about the only people whose explanation the police will accept if you exceed the legal limit in your car... If you fly a yellow flag over a centre of population you can turn it into a desert... You can tie up the traffic of any port without notice given. You can order houses, streets, whole quarters of a city to be pulled down or burnt up, and you can count on the co-operation of the nearest armed troops, to see your prescription properly carried out.'