Placebo substitution for methyldopa in geriatric hypertensive patients

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Abstract **The aim of this study was to obtain an objective evaluation of the possibly inappropriate antihypertensive therapy of elderly patients; this was done by means of placebo substitution for methyldopa, one of the drugs taken by all the participating patients.**

Forty patients were recruited from a hospital outpatient clinic and randomly allocated to two groups. One group remained on treatment which included methyldopa, while a matching placebo tablet was substituted in the other group. The study was conducted over a period of 6 months in a single-blind manner. Methyldopa was reintroduced in the placebo group when one of the evaluation clauses was recorded. Only 2 patients in the placebo group required reintroduction of methyldopa tablets. In the rest of this group there was no significant difference between systolic and diastolic pressures before and after 6 months of placebo substitution. Withdrawal of unnecessary antihypertensive therapy in the elderly should be considered. Patients must be observed carefully and therapy reintroduced when blood pressures rise.

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The extent of drug prescribing for the elderly remains an important issue, as the number of medicines prescribed tends to increase with age.[1] Persons aged over 65 years comprise a relatively small portion of the population, but ingest a disproportionate amount of drugs relative to younger adults.[2,3] Furthermore, the elderly are likely to experience adverse drug reactions two to three times more often than young adults,[3] probably because multiple disorders, altered physiological responses and variable compliance make this age group more prone to unwanted side-effects.[2] However, the incidence of adverse drug reactions correlates strongly with polypharmacy and cannot be attributed solely to changes in pharmacokinetic and pharmacodynamic responses.[4]

The drugs most commonly prescribed for the aged are diuretics and drugs that affect the cardiovascular system.[1] The treatment of hypertension in the elderly undoubtedly has benefits,[5] but the frequency of side-effects caused by antihypertensive medication warrants careful individualisation of therapy in this age group. Furthermore, in patients over the age of 80 years the risk/benefit ratio of antihypertensive treatment increases and the benefit of treatment is still disputed.[6] The aim of this study was to substitute a matching placebo for methyldopa in order to evaluate the effect of removal of a drug from the antihypertensive regimen of elderly patients without concomitantly inducing a sense of insecurity.

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Materials and methods

Forty patients over 65 years of age were recruited from a hospital outpatient clinic. Signed, informed consent was obtained from all individuals and the study protocol was approved by the Ethics Committee of the University of Pretoria.

A general medical examination which included urinalysis and electrocardiographic (ECG) evaluation, was performed at the first visit by the same investigator responsible for the follow-up examinations. Recorded entry criteria included a systolic blood pressure of not more than 160 mmHg and a maximum diastolic pressure of 100 mmHg. These blood pressure readings were confirmed on three separate occasions.

A list of random numbers was used to allocate the subjects eligible for the study into two groups of 20 patients each. One group remained on their treatment, which included methyldopa, while an identical placebo tablet was substituted for methyldopa in the other group. The rest of the prescription remained unaltered (Table I).

TABLE I.
Characteristics of patients in the two study groups*

	Methyldopa group	Placebo group
Sex (female/male)	16/2	17/1
Mean age (yrs)	75,7	76,7
	(range 65 - 90)	(range 63 - 83)
Mean mass (kg)	79,7	77,3
	(range 53 - 107)	(range 52 - 111)
No. of patients taking		
Methyldopa	18	18
Diuretics	16	13
β-blockers	2	4
Calcium antagonists	3	2
Vasodilators	0	3
ACE inhibitors	1	3
NSAIDs	10	11

* Data given for patients who completed the study.

The study was conducted in a single-blind manner. Placebo substitution commenced after the first visit. There was no wash-out period. Both groups were examined after the 1st, 2nd and 4th weeks of the study in order to detect a possible rise in blood pressure. Thereafter all patients were followed up once monthly for at least 6 months. Reintroduction of therapy was considered when one of the following occurred: systolic blood pressure > 160 mmHg, diastolic blood pressure ≥ 110 mmHg, proteinuria or dyspnoea.

The patients were at ease and sitting when blood pressure was recorded with a mercury manometer. The cuff (35 × 12 cm) was placed on the right arm. In the obese a cuff with an inflatable section 42 × 15 cm was used. Readings of the diastolic pressure were taken from the fourth Korotkoff phase.

Analysis of data

The Wilcoxon signed rank test was used to detect differences in blood pressure within the methyldopa and

TABLE II.
Comparisons between the methyldopa and placebo groups at the start and completion of the study

	Methyldopa group ($N = 18$)		Placebo group ($N = 18$)	
	Entry	Completion	Entry	Completion
Mean systolic pressure (mmHg) (± SD)	148,11 ± 12,0	143,94 ± 12,09	150,3 ± 13,13	145,1 ± 9,81
Mean diastolic pressure (mmHg) (± SD)	85,78 ± 5,17	84,72 ± 5,98	88,7 ± 6,82	89,5 ± 6,85

placebo groups respectively, while Student's *t*-statistic was used to test for differences between the two groups. Differences were considered statistically significant at the 5% level throughout.

Results

Four patients, 2 from the active and 2 from the placebo group, were withdrawn from the study because of lack of compliance and logistic reasons, e.g. moving home. Methyldopa treatment had to be reintroduced after 1 month in 2 of the remaining 18 patients in the placebo group, as a diastolic pressure of 110 mmHg was recorded in both of them. In one, methyldopa was the sole drug, while in the other the remaining thiazide diuretic was apparently inadequate.

There was no significant rise in systolic and diastolic pressures after placebo subsitution (Wilcoxon signed rank test). Furthermore, the mean systolic and mean diastolic blood pressures did not differ significantly between the placebo group and the methyldopa group at the commencement and completion of the study (Student's *t*-statistic). The mean systolic and mean diastolic blood pressures for both groups are shown in Table II.

Discussion

The treatment of hypertension is part of preventive medicine and patients are usually advised that treatment is lifelong. This assumption has been questioned and successful withdrawal of antihypertensive therapy has been accomplished in selected patients.[7] Lernfeldt *et al.*[8] also demonstrated that withdrawal of antihypertensive therapy in the elderly could be attempted, provided that these patients were free of cardiovascular disease.

In the present study 16 of the 18 patients remained normotensive during the 6 months following methyldopa withdrawal. Our findings raise questions regarding the validity of the initial assessment as well as the need for antihypertensive treatment. It is noteworthy that the prescriptions of 10 patients in the methyldopa group and 11 patients in the placebo group included non-steroidal anti-inflammatory drugs (NSAIDs). It would seem that the latter drugs, e.g. ibuprofen, could reduce the efficacy of antihypertensive therapy in patients taking various combinations of antihypertensive drugs.[9] Moreover, a recent South African survey identified diuretics and NSAIDs as chiefly responsible for unwanted side-effects in the aged.[10] Clearly critical, thoughtful prescription habits could reduce the incidence of avoidable iatrogenic illness.[11] Regular review of medication, questioning of the need for drugs and suspension of all unnecessary medication could contribute substantially to an enhanced quality of life for the elderly.

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