Effects of methyldopa on prolactin and growth hormone

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Summary

The effects of administration of methyldopa on serum prolactin and growth hormone (GH) concentrations in hypertensive patients were studied. Single doses of methyldopa (750 or 1000 mg) significantly increased serum prolactin levels, peak concentrations occurring four to six hours after drug administration. Long-term methyldopa treatment was associated with threefold to fourfold increases in basal prolactin levels compared with those in normal subjects. In patients treated with methyldopa for two to three weeks the GH response to insulin hypoglycaemia was significantly greater than in normal subjects and untreated hypertensive patients. In contrast, patients treated for prolonged periods (mean 13·4 months) had a GH response indistinguishable from normal.

Introduction

It is now well established that the monoamines dopamine, noradrenaline, and serotonin mediate between neurones in the central nervous system and hormone secretory cells of the hypothalamus.[1] Furthermore, several drugs known to influence central monoaminergic activity have been shown to alter circulating concentrations of anterior pituitary hormones whose release is under hypothalamic control.[2]

Commonly used antihypertensive drugs such as methyldopa, clonidine, and beta-adrenergic neurone blocking drugs exert their therapeutic effect at least partly via central monaminergic pathways.[3-5] Since these drugs are administered for prolonged periods in clinical practice it is of considerable importance to delineate their side effects. We studied changes in plasma concentrations of serum prolactin and growth hormone (GH) in patients given single and multiple doses of methyldopa.

Patients and methods

Thirty-two patients referred to the hypertension clinic of Hammersmith Hospital were selected for study. Informed consent was obtained for all studies and the protocols were approved by the hospital ethical committee. The patients ranged in age from 32 to 61 years, and there were 18 men and 14 women.

The blood pressure of untreated patients ranged from 180/110 to 230/120 mm Hg. None had accelerated hypertension or were in heart failure and their blood urea concentrations ranged from 5·3 to 10·0 mmol/l (30-60 mg/100 ml).

Ten patients had been taking methyldopa for at least six months (mean (±SE of mean) 13·4±8·1 months); seven were taking methyldopa as their sole treatment, while three were also taking bendrofluazide. The dose of methyldopa ranged from 0·5 to 2·25 g/day. Laboratory data for basal prolactin concentrations and the serum GH response to insulin hypoglycaemia of 16 healthy normotensive subjects on no therapy were used to establish values for normal controls.

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DESIGN OF STUDIES

Response of serum prolactin to single dose of methyldopa—Seven untreated hypertensive men (mean age 47·1±7·7 years) were admitted to hospital. On the day of the test they remained in bed from midnight and were offered no food until three hours after drug administration. At 0900 a butterfly needle was inserted into a forearm vein, and 60 minutes later blood was obtained for estimating basal serum prolactin concentrations. Methyldopa, 1000 mg (five patients) or 750 mg (two patients), was given by mouth. Blood was taken every 30 minutes for three hours and thereafter every hour for another four hours for measuring hormone concentrations and plasma methyldopa concentrations. Blood pressure was measured at similar times on the opposite arm by conventional sphygmomanometry, and the mean blood pressure was calculated as diastolic pressure plus one-third of the pulse pressure.

Response of serum prolactin to single dose of bethanidine—Two untreated hypertensive patients (one man and one woman aged 42 and 50 years respectively) underwent the same preparation as outlined above, but were given bethanidine 50 mg in a single oral dose instead of methyldopa. Bethanidine is an adrenergic neurone blocking agent with no central hypotensive component.

Response of serum prolactin to long-term methyldopa—Seven patients (four men, three women; mean age 50·4±6·8 years) who had been taking methyldopa for a mean of 13·4 months had blood samples taken for estimating basal prolactin concentrations before administration of insulin for GH response testing.

Response of serum GH to insulin hypoglycaemia—The GH response to insulin hypoglycaemia was studied in three groups of patients: (*a*) Seven untreated hypertensive patients (three men, four women; mean age 52·7±9·3 years); (*b*) 11 patients (seven men, four women; mean age 48·1±11·6 years) given methyldopa for two to three weeks and in whom satisfactory blood pressure control had been established. This group included five of the seven whose prolactin response to a single dose of methyldopa had been studied; (*c*) Ten patients (five men, five women; mean age 52·3±10·4 years) who had been taking methyldopa either alone (seven patients) or with bendrofluazide (three patients) for a mean of 13·4 months and whose blood pressure at the time of study was satisfactorily controlled. GH response in these three groups was measured after administration of insulin. Each patient reported to hospital at 0900 after fasting overnight. Patients in groups *b* and *c* had taken methyldopa between 0700 and 0800. A butterfly needle was inserted into a forearm vein, and the patient rested quietly for 45 minutes. Two blood samples were taken 15 minutes apart for estimating baseline GH and blood sugar concentrations. Soluble insulin (0·3 U/kg body weight) was given by intravenous injection, and blood was obtained at 15, 30, 45, 60, 90, and 120 minutes. All the patients became clinically hypoglycaemic, and when these symptoms persisted for more than 15 minutes 50 g dextrose was given by mouth.

ASSAYS

Serum prolactin was measured by a double antibody radioimmunoassay using antiserum 65/5 and standard human prolactin 72-4-9 supplied by Professor H Friesen. The human prolactin for labelling was supplied by the National Institutes of Health, Bethesda, Maryland (batch VLS No 1).

GH was measured by a double antibody radioimmunoassay,[6] and the results were expressed as mIU/l of the World Health Organisation first international reference preparation (66/217).

Plasma methyldopa concentrations were measured using the method of Laverty and Taylor.[7]

Blood sugar was measured by autoanalyser.

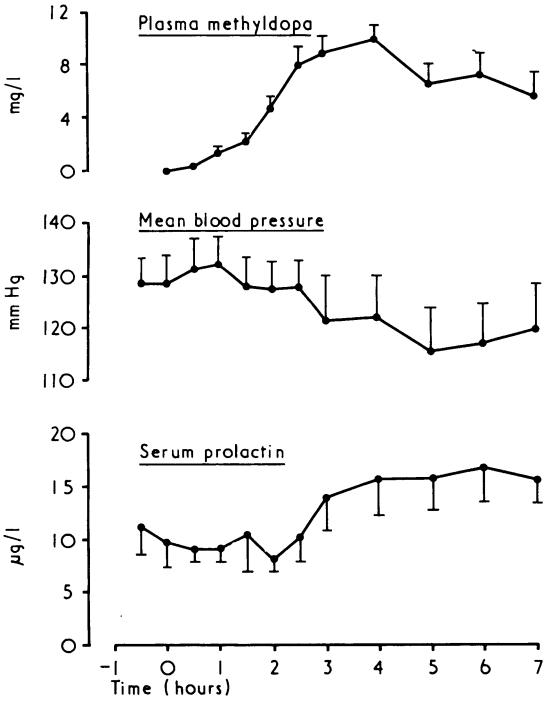
Statistical comparisons were made using Student's *t* test or the Wilcoxon rank sum test.

Results

Response of serum prolactin to single dose of methyldopa

Basal serum prolactin concentrations ranged from 5·0 to 25 μg/l (mean (±SEM) 9·9±2·5 μg/l). These values did not differ significantly from the normal values in the laboratory (6·5±2·4 μg/l). Maximal serum prolactin concentrations after methyldopa ranged from 9·2 to 40 μg/l (mean 23·0±3·8 μg/l). These maximal values occurred four to six hours after methyldopa administration, and the change between basal concentrations and maximum methyldopa-stimulated concentrations was significant ($P<0·02$). The maximum fall in the mean arterial pressure was 7-48 mm Hg ($P<0·02$) in individual patients. The maximum fall in blood pressure occurred in individual patients four to seven hours after oral dosing with methyldopa. The figure shows the mean serum prolactin concentrations and changes in blood pressure at varying times after methyldopa administration. Neither the prolactin concentration nor the blood pressure differed significantly at any one time from the group's basal value.

Maximal plasma methyldopa concentrations ranged from 4·1 to 18·6 mg/l in the seven patients. Maximum plasma methyldopa concentrations were reached two to six hours after oral dosing. The figure shows the time relation between plasma concentrations of methyldopa, serum prolactin levels, and blood pressures for the group of seven patients.



Mean (±SE) plasma methyldopa concentrations, mean blood pressures, and serum prolactin concentrations in seven patients who received oral methyldopa at time 0.

There was no significant correlation between either basal serum prolactin concentrations and initial blood pressure or the percentage rise in prolactin concentrations and the percentage fall in blood pressure in individual patients.

Response of serum prolactin to single dose of bethanidine

In two patients bethanidine administration resulted in maximum falls in mean blood pressure of 18 mm Hg and 25 mm Hg. Basal prolactin concentrations were 7·0 μg/l and 8·5 μg/l. There were no obvious changes in the serum prolactin levels of either of these patients.

Response of serum prolactin to long-term methyldopa

The basal serum prolactin concentrations in the seven patients ranged from 4·4 to 45 μg/l (mean 22·9±6·8 μg/l), which was significantly higher than the normal laboratory values (6·5±2·4 μg/l; $P<0·025$).

Response of serum GH concentrations to insulin hypoglycaemia

Untreated hypertensive patients and normal controls—The table shows the absolute values of serum GH before and during insulin hypoglycaemia in the seven untreated hypertenisve patients compared with those in 16 normal subjects. The hypoglycaemia attained was similar in both groups. There was no significant difference in GH concentrations either initially or subsequently.

Hypertensive patients on methyldopa for 2-3 weeks—The serum GH concentrations during insulin hypoglycaemia in these 11 patients were significantly greater than those achieved in the normal controls at 60 minutes ($P<0·01$), 90 minutes ($P<0·01$), and 120 minutes ($P<0·01$) (see table). Only at 90 minutes, however, were the values significantly greater than those in untreated hypertensive patients ($P<0·02$).

Hypertensive patients on methyldopa for 13·4 months—At no time after insulin administration did the GH concentrations in this group differ significantly from those of either the normotensive controls or the untreated hypertensive patients. At 60 and 90 minutes the values were significantly lower than those of patients treated for two to three weeks ($P<0·01$).

Discussion

Methyldopa administration results in depression of synthesis and subsequent depletion of the monoamines noradrenaline, dopamine, and serotonin within the brain.[8] This is probably the basis of its hypotensive effect[3 9] and, since there is much evidence linking monoamine neurotransmitters with neuroendocrine regulation, a possible reason for change in pituitary function. All anterior pituitary hormones are under hypothalamic control, which may be inhibitory or stimulatory. The release of prolactin is principally controlled by a prolactin inhibitory factor (PIF) whose structure is unknown, although there is some circumstantial evidence equating PIF with dopamine itself.[10] Certainly, administration of levodopa, the precursor of dopamine, results in a brisk and predictable fall in serum prolactin concentrations in man.[11] Moreover, Turkington[12] has shown that

Mean (±SE of mean) serum GH (mIU/l) and blood glucose (mmol/l) concentrations in controls and three groups of patients

Time (min):	0		15		30		45		60		90		120	
	GH	Glucose	GH	Glucose	GH	Glucose	GH	Glucose	GH	Glucose	GH	Glucose	GH	Glucose
Controls	4·0 ±1·09	4·27 ±0·22			13·1 ±4·9	1·33 ±0·21			66·9 ±14·5	1·83 ±0·21	66·9 ±16·8	2·61 ±0·5	31·6 ±8·8	4·61 ±1·0
Untreated hypertensive patients	2·9 ±0·8	4·33 ±0·13	2·8 ±0·9	2·27 ±0·28	7·7 ±2·6	1·05 ±0·11	71 ±11·9	1·33 ±0·17	100·7 ±31·8	1·44 ±0·28	71·1 ±19·6	2·11 ±0·4	68·6 ±29·8	2·78 ±0·49
Patients on methyldopa 2-3 weeks	4·2 ±0·9	4·33 ±0·2	4·5 ±0·9	2·66 ±0·27	22·2 ±8·7	1·44 ±0·23	114·7 ±37·7	1·50 ±0·16	171·4 ±38·0	2·03 ±0·23	162·8 ±26·2	2·55 ±0·53	86·1 ±19·2	3·77 ±0·8
Patients on methyldopa 13·4 months	3·6 ±0·05	4·22 ±0·16	3·5 ±0·8	3·39 ±0·27	5·5 ±1·5	1·33 ±0·25	46·9 ±22·1	1·55 ±0·18	1·55 ±1·24	1·67 ±0·17	78·9 ±13·8	3·22 ±0·46	75·8 ±16·4	3·6 ±0·49

Conversion: SI to traditional units—Glucose: 1 mmol/l ≈ 18 mg/100 ml.

methyldopa given for two to six weeks causes a rise in serum prolactin concentrations in hypertensive patients.

Our studies have confirmed that patients on long-term treatment with methyldopa have raised serum prolactin concentrations. Furthermore, we have shown that even a single oral dose of methyldopa will increase serum prolactin concentrations. Basal serum prolactin levels varied considerably in the seven patients who received a single dose of methyldopa, but they did not correlate with the level of blood pressure. That the rise in prolactin produced by methyldopa was not merely a result of hypotension is suggested by the results in two patients given bethanidine (which lowers blood pressure by a peripheral adrenergic neurone blocking effect); there was no change in serum prolactin concentrations in spite of a considerable fall in blood pressure.

It is difficult to assess the importance of these drug-induced changes in serum prolactin concentrations. There are considerable species differences in the effects of prolactin itself on blood pressure,[13 14] and its effect in man is unknown. Whether prolactin is a mediator of the sodium retention produced by methyldopa is also open to question.[15] Finally, galactorrhoea is seen in a few patients on methyldopa, but the relation of this to the magnitude of the prolactin response is not clear.

The control of GH secretion is relatively more complex than that of prolactin. GH secretion is modulated by catecholamines, and in man there is evidence that alpha-adrenergic stimulation increases and beta-adrenergic stimulation decreases circulating concentrations.[16] Furthermore, administration of levodopa, the precursor of dopamine, has been reported to increase circulating GH.[17] When GH secretion was measured over 24 hours in a group of Parkinsonian patients given levodopa, however, 79% of the time GH concentrations failed to rise.[18] Using insulin hypoglycaemia as the stimulus for GH secretion, the difference between patients on short-term and long-term methyldopa therapy may be explicable in terms of the time course of substitution of endogenous catecholamines with metabolites of methyldopa within the brain. There may be a similar explanation for the greater effect of methyldopa on serum prolactin levels in patients on prolonged methyldopa treatment, since, unlike GH, prolactin secretion is inhibited by catecholamines.[11]

These data suggest a novel aspect of the effects of long-term hypotensive therapy. As new, more potent, centrally acting antihypertensive drugs become available, hormonally mediated effects may become of considerable importance.

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SHORT REPORTS

Excessive egg consumption, xanthomatosis, and hypercholesterolaemia

We report a case of xanthomatosis and hypercholesterolaemia resulting from eating too many eggs.

Case report

A 30-year-old woman (51 kg, 164 cm) was admitted to hospital in 1969 for a routine check-up. She had had an appendicectomy and tonsillectomy. There was no abnormality apart from a few pinhead-sized xanthomas between the thumb and index finger on the backs of her hands. Among the serum laboratory findings increases in cholesterol (24·4 mmol/l (940 mg/100 ml)) and phospholipids (measured as lipidphosphor) 8·2 mmol/l (635 mg/100 ml)) were remarkable. The lipidelectrophoresis was typical for a type IIa hyperlipidaemia according to Fredrickson. Triglyceride concentration was 2·2 mmol/l (198 mg/100 ml).

Careful questioning showed that she had followed the dietary recommendations of a magazine for three and a half years to stay slim. Each day she had consumed eight to 12 eggs, one or two lean steaks or half a small chicken and, half to one litre of milk. Sometimes some cottage cheese or tomatoes enriched the menu and, on rare occasions, fruit. She completely avoided butter, bread, potatoes, rice, noodles, alcohol, or any other food or beverage containing carbohydrate. The daily cholesterol intake, which was mainly derived from the egg yolks, was about 3500 mg. The total calorie intake was about 8·4 MJ (2000 kcal) (35% protein, 55% fat, and 10% carbohydrates polyunsaturated fat:saturated fat (P:S) ratio=0·26). She was advised to change her diet and in particular to stop eating eggs. The total daily calorie intake remained the same (22% protein, 35% fat, and 43% carbohydrate, P:S ratio=0·30) but eggs were completely avoided. The daily cholesterol intake dropped to 235 mg. After 16 days the serum cholesterol was 19·4 mmol/l (750 mg/100 ml), triglycerides 2·9 mmol/l (261 mg/100 ml), and phospholipids 6·1 mmol/l (474 mg/100 ml). In the following years the serum cholesterol was checked several times by a doctor and reported to be in the normal range. In September 1974 no lipid deposits were found on the skin, cholesterol was 4·9 mmol/l (188 mg/100 ml), triglycerides 1·8 mmol/l (157 mg/100 ml), and phospholipids 4 mmol/l (310 mg/100 ml). The lipidelectrophoresis was normal. The phospholipids were still somewhat above normal, which may have been connected with an oestrogen medication the patient had received.

Comment

Man and Andrus[1] produced high blood cholesterol levels in an adult macaccus rhesus monkey fed on a diet rich in egg yolks. After two-and-half years on this regimen the monkey developed xanthomatosis and when killed a year later exhibited extensive atherosclerosis. Similar results were reported by Gresham *et al*.[2] The chief effect of the atherogenic diet was the increase in the β-lipoproteins and their cholesterol and phospholipid content, but there was no increase in triglycerides. These findings agree with our observations in men. This case report also confirms the observation of Connor *et al*,[3] who showed the single influence of a diet rich in egg yolks on serum cholesterol levels in men under metabolic ward conditions. They