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DRUG METABOLISM AND LIVER FUNCTION AFTER METHYLDOPA WITHDRAWAL

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1 The effects of methyldopa withdrawal on liver function and drug metabolism were investigated in ten elderly females suffering from the drug-induced orthostatic reaction and resistant hypertension.

2 There was a significant increase in serum albumin level, antipyrine metabolism and urinary excretion of D-glucaric acid 6 months after the methyldopa withdrawal.

3 The results suggest that patients treated with methyldopa might show a reduced metabolizing ability in spite of normal liver function tests.

Introduction

Therapy with methyldopa has been associated with the development of hepatic injury. The drug is oxidized by cytochrome P-450-generated superoxide anion into a semiquinone and a quinone, and these reactive intermediates, by binding covalently with macromolecules, may damage the liver (Dybing, Nelson, Mitchell, Sasame & Gillette, 1976). Impaired liver drug metabolism of this kind has been reported in experimental animals and healthy volunteers treated with methyldopa (Gachályi, Káldor & Tihanyi, 1978) and in patients with methyldopa-induced liver injury (Sotaniemi, Hokkanen, Ahokas, Pelkonen & Ahlqvist, 1977). This suggests that therapy with methyldopa may interact with the metabolism of other compounds.

Little is known about hepatic drug metabolism after methyldopa withdrawal, a problem which one faces when selecting appropriate antihypertensive treatment for patients suffering from methyldopa-induced orthostatic reactions and resistance to the drug. The problem was evaluated by performing liver function tests and determining indices of drug metabolism (oral antipyrine test, urinary excretion of D-glucaric acid) in a group of elderly females during treatment with methyldopa and again 6 months after discontinuation of the drug.

Methods

Subjects

Ten females with methyldopa-induced orthostatic reaction or resistant hypertension were investigated (Table 1). They had all been referred to the Clinical Research Unit by physicians at the Oulu Community Health Centre, having had elevated blood pressure for 4 to 30 years, and having developed orthostatic reactions (cases 1–4 and 8–10) and resistant hypertension (cases 5–7) during recent treatment with methyldopa (Sembrina^{R}). All the patients had also received digoxin, and all but two (cases 7 and 9) had been given diuretics (thiazides and frusemide). Five subjects (cases 3, 6, 7, 8 and 9) were diabetics and received oral antidiabetic drugs. At the time of present study heart failure was compensated and kidney function was normal in all but two patients (cases 3 and 5 had serum creatinine levels 127 μmol/l and 197 μmol/l). The patients were on a standard hospital diet for 3 days before the drug metabolism studies. Informed consent was obtained from each subject before the antipyrine test was performed.

Protocol

Blood samples for the liver function tests were drawn after an overnight fast, and 20 mg/kg of antipyrine dissolved in 100 ml of fruit juice, was administered to the patients immediately. Plasma specimens were obtained by venepuncture before and 1, 3, 6, 9, 12 and 24 h after drug administration. A second antipyrine test was then performed in the sixth month after methyldopa withdrawal. All other drug therapy was kept unchanged, except that three patients now needed clonidine for blood pressure control (cases 4, 5 and 7).

Analytical methods

Antipyrine assay Plasma antipyrine concentration was determined by the gas-liquid chromatography method (Prescott, Adjepon-Yamoah & Roberts, 1973) used previously in this Research Unit

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Table 1 Clinical and biochemical data and antipyrine half-life in ten females treated with methyldopa

	Body			*Hypertension*			*Liver function tests**						*Urinary* D-*glucaric acid***	*Antipyrine half-life****
Patient	*Age (years)*	*Height (cm)*	*Weight (kg)*	*Reasons for admission*	*Duration (years)*	*Dose of methyldopa (mg/day)*	*Total bilirubin (μmol/l)*	*A-P (U/l)*	*ALAT (U/l)*	*ASAT (U/l)*	*ALB (g/l)*	*ASMA*	*μmol/day*	*(h)*
1	61	153	66.5	Orthostatic reaction	20	750	9	179	29	17	44	–	13.6	10.4
2	63	155	87.5	Orthostatic reaction	10	500	6	175	43	18	41	–	11.7	18.0
3	68	152	100.0	Orthostatic reaction	10	1000	6	519****	20	10	45	–	11.4	18.8
4	69	142	48.0	Orthostatic reaction	10	1000	11	178	28	19	43	+	20.5	8.4
5	70	153	53.5	Resistant hypertension	30	750	5	245	34	27	42	–	67.5	10.2
6	75	149	75.0	Resistant hypertension	25	750	9	108	16	11	39	–	9.5	15.4
7	76	152	67.0	Resistant hypertension	10	250	9	158	30	14	39	+	15.8	17.2
8	79	151	60.0	Orthostatic reaction	10	500	6	65	13	14	47	–	28.0	11.8
9	84	146	69.0	Orthostatic reaction	14	750	8	126	26	18	44	+	26.7	13.8
10	84	155	74.0	Orthostatic reaction	4	750	7	123	10	21	41	–	15.0	13.2

* A-P = alkaline phosphatase (normal value in our laboratory < 250 U/l)
ALAT = alanine transferase (< 40 U/l)
ASAT = aspartate transferase (< 40 U/l)
ALB = albumin (> 40 g/l)
ASMA = smooth muscle antibodies
** Urinary D-glucaric acid, μmol 1,4-glucaro lactone/day (8.0–24.0)
*** Antipyrine half-life (6.5–12.5 h)
**** bone origin

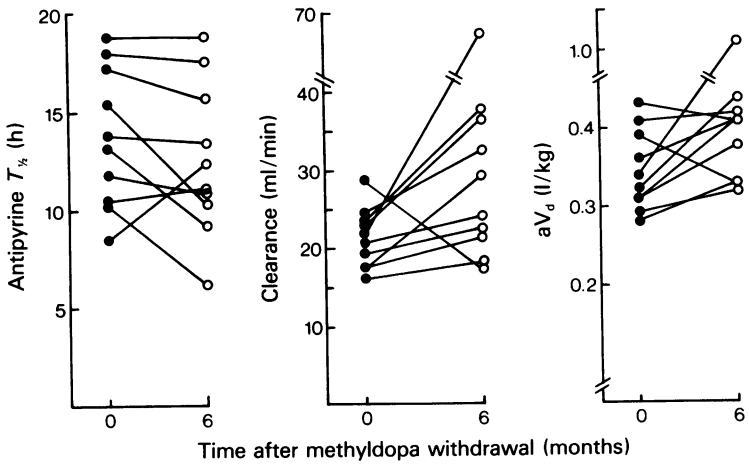

Figure 1 Change in antipyrine kinetics after methyldopa withdrawal

(Sotaniemi, Ahlqvist, Pelkonen, Pirttiaho & Luoma, 1977).

Urinary D-*glucaric acid* was assayed by an enzymatic method based on that of Marsh & Carr (1965), as used earlier (Sotaniemi, Medzihradsky & Eliasson, 1974), and expressed as μmol of glucaro-1-4-lactone/24 h.

Liver function tests Serum albumin concentration, total bilirubin concentration, aspartate transferase (ASAT, SGOT), alanine transferase (ALAT, SGPT) and alkaline phosphatase (A-P) activities were measured using standard Autoanalyzer techniques (SMAC analyzer, Technicon Instrument Corporation, Tarrytown, N.Y.). Smooth muscle antibodies (ASMA) were determined by indirect immunofluorescence (Bottazzo, Fiorin-Christensen, Grandville Swana, Doniach & Grobschel-Stewart, 1976).

Calculations The plasma elimination half-life ($T_{\frac{1}{2}}$) was calculated from the linear portion of the log concentration/time curve. Plasma clearance (Cl) was obtained by dividing the dose by the area under the plasma concentration/time curve calculated by the trapezoidal rule. The apparent volume of distribution (aV_d) was calculated from the relationship: $aV_d = Cl/k$, where k is the elimination rate constant. The statistical analysis of the data employed the Student's *t*-test.

Results

Three patients (cases 5, 6 and 7) had resistant hypertension and seven (cases 1–4 and 8–10)

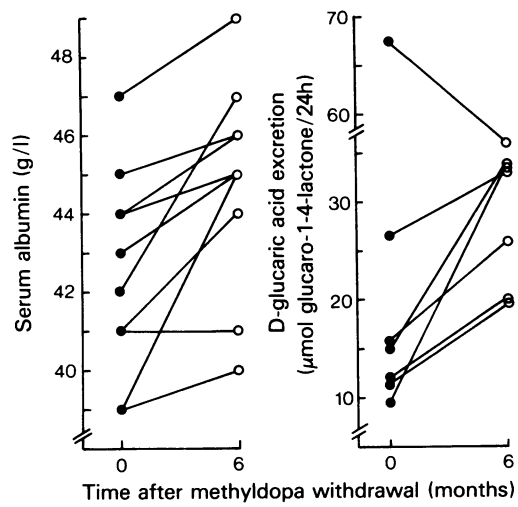

Figure 2 Change in serum albumin levels and urinary excretion of D-glucaric acid after methyldopa withdrawal.

orthostatic reactions as the reason for admission to hospital. Methyldopa had been used with an average dose of 700 mg/day (range 500 to 1000 mg/day). The liver function tests varied within the normal range, except for one patient (case 2) with a slightly elevated ALAT value (Table 1).

Withdrawal of methyldopa brought about an improvement in drug metabolism and protein synthesis (Figures 1 and 2, Table 1). The serum albumin level increased in all subjects, whereas the values for the other liver tests remained unchanged.

Table 2 Antipyrine metabolism and liver function tests in ten females on methyldopa and 6 months after the drug withdrawal

		Antipyrine				*Liver function tests*						
	Body weight (kg)	*$T_{\frac{1}{2}}$ (h)*	*Cl (ml/min)*	*aV_d (l/kg)*	*Total bilirubin µmol/l*	*A-P (U/l)*	*ALAT (U/l)*	*ASAT (U/l)*	*ALB (g/l)*	*ASMA positive cases*	*Urinary D-glucaric acid (µmol/day) (n=7)*
On methyldopa											
Mean	70.0	13.7	20.3	0.34	7.6	187.6	24.9	16.9	42.5	3/10	22.5
s.d.	15.4	3.6	2.9	0.05	1.9	126.3	10.2	5.0	2.6		20.6
Six months after methyldopa withdrawal											
Mean	68.5	12.5	32.4*	0.45	7.7	206.8	23.7	19.4	44.8**	0/10	32.0*
s.d.	13.9	3.9	15.0	0.22	2.0	100.4	9.9	3.8	2.7		12.7

P values for difference between means: * < 0.05, ** < 0.005
Cl = Plasma clearance
aV_d = the apparent volume of distribution

Antipyrine metabolism improved in nine of the ten patients. Urinary D-glucaric acid excretion increased in six of the seven patients for whom both urinary collections were available. Smooth muscle antibodies become negative in the three cases with positive readings (Table 1).

The half-life of antipyrine in our control material (Sotaniemi, Pelkonen, Ahokas, Pirttiaho & Ahlqvist, 1978), thirteen subjects with normal liver histology, was 7.9 (s.d. 2.1) h and its clearance rate 49.3 (25.6) ml/min. Comparison of the values for the subjects on methyldopa with these reference values revealed significant differences.

None of the patients showed any hypertensive symptoms after methyldopa withdrawal.

Discussion

While therapy with methyldopa has been associated with a decrease in hepatic cytochrome P-450 content in both animals and man (Gachályi *et al.*, 1978; Sotaniemi, Hokkanen *et al.*, 1977), the changes in drug metabolism parameters and serum albumin levels noted here suggest an increased activity of the mono-oxidase enzyme system after methyldopa withdrawal. All but one of the present patients had normal liver function while being treated with methyldopa, but the improvement in drug metabolism after withdrawal suggests that subjects treated with this antihypertensive agent may have a reduced detoxication ability in spite of such normal values in liver tests.

The hepatotoxicity of methyldopa is manifested in two forms, as a hypersensitive-type reaction and as a chronic active disease, like hepatitis (Toghill, Smith, Bento, Brown & Matthews, 1974; Maddrey & Boitnott, 1975; Sotaniemi, Hokkanen *et al.*, 1977). Since the former type of reaction occurs only in a few patients treated with methyldopa, the possible mechanisms may be increased sensitivity to the causative intermediate or enhanced production of the latter associated with underlying genetic factors. Chronic liver damage takes several years to develop (Sotaniemi, Hokkanen *et al.*, 1977), and the present findings suggest that reduced hepatic drug ability acts as a preceding factor for this.

High blood pressure leads to increased morbidity and mortality, and the control of hypertension results in improvement compared with no treatment (United States Veterans Administration, 1967, 1970). However, in the treatment of elderly people maintenance of blood flow in brain, heart and kidney must be considered. In addition, the old ones are more sensitive to potent antihypertensive drugs than young people and symptoms such as orthostatic reactions, drowsiness, collapse, blurred vision and

convulsions may occur. In this study blood pressure of the seven female patients, previously treated with methyldopa, could be controlled with diuretics, and only three also needed clonidine.

The alteration in drug metabolism with time after methyldopa, as seen here, suggests the need to focus attention on the heptic handling of drugs when selecting appropriate antihypertensive therapy for elderly people after the withdrawal. The reduced drug metabolizing capacity associated with methyldopa therapy can also be regarded as an extra risk for elderly people known primarily to have a low ability to hydroxylate foreign compounds (O'Malley, Crooks, Duke & Stevenson, 1971).

Our patients were old females and therefore probably not representative for hypertensive subjects in general in terms of age, concomitant illness or drug therapy. However, changes in drug metabolism parameters and serum albumin levels were similar in all but one case. We have also obtained similar changes in young subjects after discontinuation of methyldopa. The possibility of altered drug metabolism after the drug withdrawal should hence be considered.

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