still desire sexual fulfilment and many even seek a further marriage. Mating theories are against her finding a future stable relationship.[9] Few men want the responsibility of other people's children, especially if disturbed. At an age of 30 and with these handicaps she cannot afford to be too selective about her partners. Patient guidance and support is essential to see even the more able and intelligent woman through this difficult period.

A few women present as extremely damaged personalities who will need long-term support with their children. Often they need protection against their own stimulus-seeking activities. Though they flinch from violence like other people they have the ability to seek violent men or by their behaviour to provoke attack from the opposite sex.

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Clinical Trials

Effect of Different Doses of Chlorthalidone on Blood Pressure, Serum Potassium, and Serum Urate

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Summary

Chlorthalidone given to 40 hypertensive women significantly decreased blood pressure and serum potassium levels and increased the serum urate concentration. There were no individual correlations between the reduction in blood pressure and the decrease in serum potassium or the increase in serum urate. A reduction in dosage from 50 mg daily to 50 mg three times a week produced no significant changes in the diastolic or mean blood pressures though the systolic blood pressure was moderately increased. Concomitantly, serum potassium increased and serum urate decreased significantly on the lower chlorthalidone dose. We conclude that high doses of oral diuretics compared with lower ones are of limited further benefit and may increase the risk of clinically significant hypokalaemia and hyperuricaemia.

Introduction

Since the first favourable reports of the antihypertensive effect of oral diuretics[1 2] these agents have been widely used for the treatment of arterial hypertension. In Göteborg, for example, 15% of all women aged 60 years were found to be receiving such treatment.[3]

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In hypertensive cardiovascular disease oral diuretics produce a flat dose-response curve, the main fall in blood pressure occurring after a relatively low dose.[4] Side effects such as decreased serum potassium and increased serum urate levels have been recognized,[1 2 5 6] though these may be partly caused or accentuated by the routine use of oral diuretics in high doses without adjustment to the needs of the patient. We have therefore studied the effects of two dose levels of chlorthalidone on blood pressure and related these to the side effects.

The mode of action of oral diuretics such as chlorthalidone is not fully understood. It has been suggested, for example, that some hypokalaemia is a prerequisite for achieving an optimal hypotensive effect.[7] We have therefore also examined the relation between the influence of chlorthalidone on blood pressure and the serum potassium levels.

Materials and Methods

During a population-screening survey[8] 40 women were found repeatedly to have systolic pressures of 160 mm Hg or more and diastolic pressures above 95 mm Hg. None were on antihypertensive treatment. Then they took part in a trial comparing the effects of an adrenergic β-receptor blocking agent—alprenolol (Aptin)—and chlorthalidone (Hygroton).[9] These drugs were given for three-month periods using a double-blind, crossover technique, placebo being used for the month before the active treatment and again for one month between the active treatments. Chlorthalidone was given in single daily doses of 50 mg. Supplementation with potassium chloride 0·75 g twice daily was used throughout.

Eleven women continued to take chlorthalidone after completing the trial and were subsequently examined at intervals of two to four months. During that period the dose was reduced to 50 mg three times a week. The potassium supplementation remained unchanged. They received the higher dose of chlorthalidone for 3 to 13 (mean 4·5) months and the lower dose for 2 to 10 (mean 5·7) months.

Examinations during treatment with the high and low doses were carried out at the same time of day. During the low-dose period the patients were examined the day after taking the tablets. Blood pressure was measured after about 10 minutes' rest with the patient seated, on each occasion by the same examiner using the same mercury manometer. Mean blood pressure was calculated as the diastolic pressure plus one-third of the pulse pressure. Blood samples were taken under standardized conditions in all cases. Laboratory analyses were performed according to the routine methods of the Central Laboratory Sahlgrenska University Hospital, serum potassium by flame photometry, and serum urate by an enzymatic method.[10]

Conventional statistical methods were used for the calculation of mean values, standard errors of the means (S.E. of mean), and correlation coefficients (r). The significance of differences between paired observations was estimated using Student's *t* test. Values of $P < 0.05$ were regarded as significant.

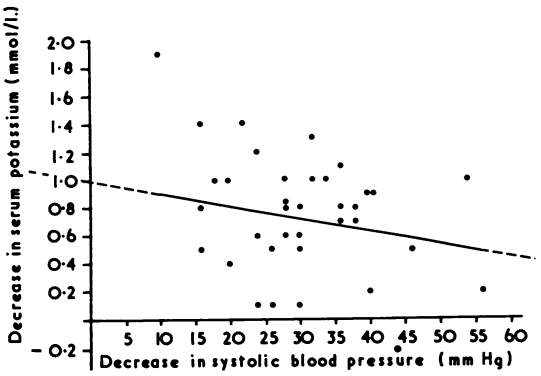

FIG. 1—Decrease in systolic blood pressure during treatment with chlorthalidone in relation to decrease in serum potassium.
Regression equation: $y = -0.0088x + 0.98$; $r = -0.20$.
Conversion: SI to Traditional Units—Potassium: 1 mmol/l. = 1 mEq/l.

Results

The mean values for blood pressure, serum potassium, and serum urate after three months on chlorthalidone were highly significantly different from those recorded during the placebo period (table I). No correlation was found between the decrease in blood pressure and the decrease in serum potassium levels or between the decrease in blood pressure and the rise in serum urate levels (figs. 1 and 2). In fact, there was a tendency towards a negative correlation between the decrease in blood pressure and the decrease in serum potassium.

The individual blood pressures and serum potassium and urate levels during the periods of high and low dosage are shown in table II. On average the systolic blood pressure was 9 mm Hg higher on the low dose ($P < 0.05$) though no significant differences were found for the diastolic and mean pressures. Serum potassium was significantly higher ($P < 0.01$) and serum urate significantly lower ($P < 0.05$) when on the low dose.

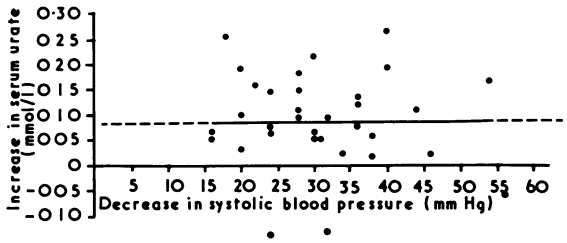

FIG. 2—Decrease in systolic blood pressure during treatment with chlorthalidone in relation to increase in serum urate.
Regression equation: $y = 0.0006x + 1.43$; $r = 0.004$.
Conversion: SI to Traditional Units—Urate: 1 mmol/l. ≈ 17 mg/100 ml.

TABLE I—*Arterial Blood Pressure and Serum Potassium and Urate Levels after One Month on Placebo Followed by Three Months on 50 mg Chlorthalidone Daily*

	No. of Patients	Placebo		Chlorthalidone		Significance Levels of Paired Differences
		Mean	S.E. of Mean	Mean	S.E. of Mean	
Systolic blood pressure (mm Hg)	40	165	3	136	2	P<0·001
Diastolic blood pressure (mm Hg)	40	102	1	90	1	P<0·001
Mean blood pressure (mm Hg)	40	123	2	105	2	P<0·001
Serum potassium (mmol/l)	39	4·1	0·04	3·4	0·1	P<0·001
Serum urate (mmol/l)	36	0·226	0·011	0·309	0·011	P<0·001

Conversion: SI to Traditional Units—Potassium: 1 mmol/l = 1 mEq/l. Urate: 1 mmol/l. ≈ 17mg/100 ml.

Discussion

The half life of chlorthalidone is about 60 hours.[11] Thus the drug may be administered once a day or every other day with small fluctuations of the plasma level between doses under steady-state conditions. In addition such a convenient mode of administration will probably also reduce the risk of failure to take the tablets.

TABLE II—*Systolic, Diastolic, and Mean Blood Pressures (in mm Hg); Serum Potassium (in mmol/l.); and Serum Urate (in mmol/l.) at Initial Population Study Examination before Antihypertensive Treatment and during Periods of Chlorthalidone Treatment in Different Doses. Levels of Significance for Paired Differences between two Treatment Periods with Chlorthalidone are Shown*

Case No.	Initial Values BeforeTreatment					Chlorthalidone 50 mg Daily					Chlorthalidone 50 mg Thrice Weekly				
	B.P.			Serum Potassium†	Serum Urate	B.P.			Serum Potassium	Serum Urate	B.P.			Serum Potassium	Serum Urate
	Systolic	Diastolic	Mean			Systolic	Diastolic	Mean			Systolic	Diastolic	Mean		
1	184	116	139	3·6	0·297	118	70	86	3·1	0·380	134	86	102	3·7	0·267
2	234	118	157	4·0	0·166	166	98	121	3·2	0·374	174	98	123	3·6	0·267
3	168	108	128	3·8	0·238	122	86	98	3·0	0·440	144	86	105	3·4	0·446
4	172	114	133	3·1	0·208	128	96	107	4·0	0·273	136	98	111	3·9	0·178
5	198	130	153	4·1	0·148	134	104	114	3·9	0·321	126	94	105	4·2	0·339
6	184	108	133	4·0	0·357	128	82	97	3·3	0·362	142	86	105	3·8	0·357
7	192	116	141	4·3	0·190	136	86	103	3·1	0·243	148	84	105	3·2	0·249
8	174	100	125	4·0	0·196	146	88	107	3·4	0·220	154	86	109	3·3	0·243
9	214	134	161	3·6	0·154	142	92	109	3·1	0·386	144	88	107	3·6	0·362
10‡	168	92	117	4·0	0·166	160	84	109	3·4	0·339	145	85	105	3·8	0·220
11‡	182	98	126	4·3	0·267	138	94	109	3·5	0·416	176	108	131	4·1	0·327
Mean ± S.E. of Mean	191±7	116±4	138±4	3·9±0·1	0·220± 0·017	136*±5	89 (N.S.) ±3	105 (N.S.) ±3	3·4**±0·1	0·345* ±0·023	145±5	90±2	110±3	3·7±0·1	0·297± 0·023

*P<0·05
**P<0·01.
†Without potassium supplementation
‡Blood pressures are not included in means as they were not measured under identical circumstances.
N.S. = Not significant.

The antihypertensive, hypokalaemic, and hyperuricaemic effects of chlorthalidone seen in previous studies were also found in the present series. The degree of antihypertensive effect obtained is probably misleadingly low because some of the women had taken chlorthalidone during the interval between the population study and the placebo period preceding the crossover study. Furthermore, half of the women had started the crossover study with alprenolol, and there seems to be a carry-over effect with both alprenolol and chlorthalidone lasting for over a month after withdrawal.[9] On the other hand, one month on placebo seems to be enough to approximate the pre-treatment values for serum potassium and serum urate.[9] In the present study potassium supplements in constant dosage were given throughout and comparison could therefore be made between the periods on different chlorthalidone doses.

The systolic blood pressure was reduced in all 40 subjects when taking chlorthalidone. Serum potassium was lower in all but one and serum urate was higher in all but three. The findings of a simultaneous reduction of mean values for blood pressure and serum potassium, as also seen in previous studies,[4 12] may lead to the assumption of a positive correlation between changes in blood pressure and serum potassium. When studying intraindividual differences, however, no such correlation was found—if anything, there was a weak negative correlation. This relation indicates that a decrease in serum potassium is not decisive for an antihypertensive effect of oral diuretics as was suggested by, for example, Grieble and Johnston.[7] Similarly, no correlation was found between individual decreases in blood pressure and increases in serum urate.

Compared with the initial value the mean blood pressure decreased by 20% during treatment with 50 mg chlorthalidone three days a week but there was a further reduction of only 4% when the dose was 50 mg daily. Even though the clinical check-ups after the initial examination may per se have been responsible for part of the reduction in blood pressure clearly the main effect was due to chlorthalidone. Compared with the initial values serum potassium was 5% lower during treatment with the lower dose of chlorthalidone and a further 8% lower with the higher dose. Serum urate was 35% higher on the lower dose and a further 22% higher on the higher one. These results might indicate that the antihypertensive effect is less dose-dependent than the effect on serum potassium and serum urate.

The comparison between high and low doses of chlorthalidone was made in only a few subjects. This part of the study was not carried out with a double-blind, crossover design and conclusions must therefore be drawn with caution. A carry-over effect from the higher dose of chlorthalidone might have influenced the results though the periods of treatment should have been long enough to exclude such a bias.

The present results agree closely with our observations in a series of 10 hypertensive patients studied under less strictly controlled conditions at a hypertension clinic.[13] (For the mean values of these observations see table III.) Furthermore, a study with hydrochlorothiazide indicated that both the antihypertensive and hypokalaemic effects were dose-dependent.[4] In that study most of the antihypertensive effect was reached at a low-dose level, and the mean blood pressure was reduced by only about 5% when the dose of hydrochlorothiazide was increased from 25 to 100 mg daily. Serum potassium, on the other hand, was about 10% lower.

TABLE III—*Duration and Type of Treatment, Arterial Blood Pressure, and Serum Potassium Levels in 10 Hypertensive Subjects Treated with Chlorthalidone in High (Mean 50 mg/Day) and Low (Mean 23 mg/Day) Doses*

	High Dose	Low Dose
Duration of treatment (months)	11·0	9·5
Potassium supplementation (g/day)	2·0	1·3
Systolic blood pressure (mm Hg)	155	152
Diastolic blood pressure (mm Hg)	97	98
Mean blood pressure (mm Hg)	116	116
Serum potassium (mmol/l.)	3·2	3·7

Conclusion

Oral diuretics are efficient as antihypertensive agents but should not be used uncritically in fixed and unnecessarily high doses. Thus high doses compared with lower ones seem to be of limited further benefit and might increase the risk of hypokalaemia and hyperuricaemia. A more individualized dosage regimen of oral diuretics is therefore recommended in the treatment of arterial hypertension.

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