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# Double-Blind Comparison of Triamterene Plus Hydrochlorothiazide and Spironolactone Plus Hydrochlorothiazide in the Treatment of Hypertension

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THE effectiveness of diuretics in the treatment of hypertension is well established, and the thiazides are probably the most widely used and accepted oral diuretic antihypertensive drugs. Continuous use of thiazides may, however, cause hypokalemia; and, therefore, potassium supplements or a potassium-sparing diuretic, either triamterene or spironolactone, are frequently prescribed concomitantly. A combination product containing triamterene plus hydrochlorothiazide has been reported to effectively lower blood pressure and conserve potassium in hypertensive patients.<sup>1</sup> Similar results have been reported with a combination of spironolactone and hydrochlorothiazide.<sup>2</sup> However, the two combinations have never been compared to each other. Therefore, a multi-investigator, double-blind study was

carried out in which the combination of 50 mg triamterene plus 25 mg hydrochlorothiazide (Dyazide\*) was compared to a combination of 25 mg spironolactone plus 25 mg hydrochlorothiazide (Aldactazide†).

## Material and Methods

*Study Group.* Each of five investigators agreed to study adult outpatients having mild to moderately severe hypertension who would normally receive antihypertensive medication. They were asked to exclude patients having any major disease or defect, other than essential hypertension, as well as patients having progressive renal dysfunction, hyperkalemia, anuria, or severe or progressive liver disease, or who were sensitive to hydrochlorothiazide, triamterene, or spironolactone.

*Study Plan.* Patients were carefully examined before they were admitted to the

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\* Smith Kline & French Laboratories, Philadelphia, Penn.

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DIURETICS IN HYPERTENSION

**TABLE I**  
Global Efficacy\*

Investigator	Satisfactory responses (no. of pts)	
	Triamterene + HCT	Spiro- lactone + HCT
A	7 (10)	8 (10)
B	6 (7)	7 (8)
C	7 (10)	7 (10)
D	10 (10)	9 (9)
E	6 (7)	4 (7)
	36 (44)	35 (44)

\* Figures in parentheses denote number of patients for whom Global Efficacy was recorded.

study. Previous antihypertensive medication was discontinued and a placebo substituted for four weeks. Any patient whose blood pressure did not increase during this four-week period was not admitted to the study. Placebos could also be administered to newly diagnosed hypertensive patients who had not previously received antihypertensive medication. At the end of this four-week period, BUN, uric acid, and serum potassium levels were determined, and a complete blood count was made.

Then, patients were randomly assigned to treatment with the combination of triamterene plus hydrochlorothiazide or the combination of spironolactone plus hydrochlorothiazide for eight weeks. Both

active medications were prepared in identical-appearing capsules so that neither the patient nor the investigator knew which medication was being taken by which patient. The dosage was one capsule b.i.d. which could be decreased or increased to a maximum of four capsules daily, depending on the patient's response.

The patients were asked to return every two weeks during the eight-week study period. At each visit, standing and supine blood pressures, were determined and recorded. BUN, uric acid, and serum potassium levels were repeated at the fourth and eighth weeks of the study, and the CBC was repeated at the end of the eight-week period.

Supplemental potassium was not prescribed for any patient. Patients whose potassium levels decreased to 3 mEq/liter or increased to 5.8 mEq/liter were dropped from the study.

*Evaluation Criteria.* Changes in blood pressure and laboratory values were the primary evaluation criteria. In addition, the investigators were asked to complete a Global Evaluation, using the following criteria: Satisfactory meant that there had been a significant decrease in systolic and diastolic blood pressures and significant alleviation of symptoms; unsatisfactory meant that there had been no significant decrease in systolic or diastolic blood pressure and little or no symptomatic relief.

**TABLE II**  
Standing Blood Pressure

	Predrug value	On-drug values			
		Week 2	Week 4	Week 6	Week 8
Triamterene + HCT	164/104	150/98	149/100	145/95	146/94
Spiro-lactone + HCT	163/108	151/98	147/97	145/96	143/96

**TABLE III**  
Supine Blood Pressure

	Predrug value	On-drug values			
		Week 2	Week 4	Week 6	Week 8
Triamterene + HCT	166/105	154/98	154/98	151/95	150/96
Spironolactone + HCT	166/109	155/99	149/94	149/96	146/96

**Results**

Data were obtained on 101 patients; however, six patients dropped out during the placebo phase and three others dropped out during the active medication phase before adequate data could be obtained. Therefore, data suitable for analysis were obtained for 92 patients (46 on each drug). In the triamterene-plus-hydrochlorothiazide group, there were 25 women and 21 men, aged 30-76 years; and in the spironolactone-plus-hydrochlorothiazide group, there were 22 women and 24 men, aged 28-84 years. Table I shows the number of patients for whom Global Efficacy was reported by each investigator. The overall Global Efficacy was

similar for both drugs: 36/44 (82 per cent) for the triamterene-plus-hydrochlorothiazide group and 35/44 (80 per cent) for the spironolactone-plus-hydrochlorothiazide group.

Patients treated with both drugs showed a decrease in blood pressure compared to their predrug values. Tables II and III show the on-drug blood pressure values by covariance analysis. In all analyses, the predrug values refer to the reading taken at the end of the placebo or no-drug period, immediately preceding the drug treatment. There were no significant differences in blood pressure readings between the two drug groups at any interval.

**TABLE IV**  
Blood Chemistry

	Predrug value	On-drug values	
		Week 4	Week 8
<b>BUN</b>			
Triamterene + HCT	17.0	21.9	22.9
Spironolactone + HCT	17.2	20.9	21.6
<b>Uric Acid</b>			
Triamterene + HCT	6.53	7.56	7.94
Spironolactone + HCT	6.54	7.82	7.73
<b>Serum Potassium</b>			
Triamterene + HCT	4.16	4.29	4.10
Spironolactone + HCT	4.28	4.25	4.22

DIURETICS IN HYPERTENSION

TABLE V  
Hematology

	Triamterene + HCT		Spironolactone + HCT	
	Pre-drug	On-drug	Pre-drug	On-drug
Hematocrit	42.9	42.6	42.7	42.5
Hemoglobin	13.9	13.9	13.8	14.4
Lymphocytes	34.6	34.3	34.5	33.8
Neutrophils	59.2	59.1	58.6	59.2
WBC	6.7	6.7	7.1	6.6
RBC	4.8	4.8	4.7	4.8

As Tables IV and V show, there were no significant differences between the two drug groups in blood chemistry or hematology values.

*Adverse Effects.* In the triamterene-plus-hydrochlorothiazide group, 13 patients reported 19 adverse effects; and in the spironolactone-plus-hydrochlorothiazide group, 12 patients reported 14 adverse effects. Headache, dizziness, and weakness were the adverse effects reported

most frequently by patients in both drug groups. Therapy was discontinued in one patient in each group because of adverse effects, i.e., a patient in the triamterene-plus-hydrochlorothiazide group who had gastrointestinal and leg cramps, and a patient in the spironolactone-plus-hydrochlorothiazide group who developed diarrhea. The adverse effects reported by each investigator for each drug are shown in Table VI.

TABLE VI  
Adverse Effects\*

	Triamterene + HCT						Spironolactone + HCT					
	A	B	C	D	E	Total	A	B	C	D	E	Total
Headache	3		3		1	7	3		2			5
Dizziness	1	1	3			5			2			2
Weakness	3	1			1	5	2					2
Diarrhea						0	1					1
Dysuria						0		1				1
Nausea						0		1				1
G.I. cramps			1			1						0
Leg cramps			1			1				1		1
Rash						0			1			1
Total	7	2	8	0	2	19	6	2	5	1	0	14

\* A, B, C, D, E are the individual investigators to whom the adverse effects were reported.

**Summary**

The results from this double-blind, multi-investigator study showed that a combination of 50 mg triamterene plus 25 mg hydrochlorothiazide and a combination of 25 mg spironolactone plus 25 mg hydrochlorothiazide were equally efficacious in lowering blood pressure in hypertensive outpatients, and that they produced the same type and incidence of adverse effects. Likewise, the two drug combinations produced similar effects on blood chemistry and hematology. There were no significant

differences between the two combination drugs in efficacy, laboratory studies, or adverse effects.

**References**

1. Heath, W. C., and Freis, E. D.: Triamterene with hydrochlorothiazide in the treatment of hypertension. *J.A.M.A.* 186:119 (1963).
2. Settel, E.: Further experience with spironolactone-hydrochlorothiazide (Aldactazide-A) in the long-term treatment of refractory cardiac edema. *J. Amer. Geriat. Soc.* 13: 655 (1965).

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