Duration of effect of single daily doses of reserpine and hydroflumethiazide evaluated by noninvasive technology in hypertensive patients

Ray W. Gifford, Jr., M.D.
Department of Hypertension and Nephrology

George W. Williams, Ph.D.
Department of Biostatistics

Donald G. Vidt, M.D.
Kennith Bolen, M.S.
Christine Acker, R.N.
Department of Hypertension and Nephrology

Reserpine's long-lasting antihypertensive action is advantageous in the treatment of the chronically ill who can take medication only once a day. To evaluate the 24-hour effect on blood pressure of single doses of reserpine (0.125 mg) and hydroflumethiazide (50 mg) combined in one tablet (Salutensin), an ambulatory blood pressure monitor was used that automatically measures and records blood pressure every 7.5 minutes for 26 hours.

Methods and materials

Data are derived from 21 patients with primary (essential) hypertension who completed the protocol. There were 15 men and 6 women; 12 were black and 9 white. Ages ranged from 32 to 74 years (mean, 54 years). Hypertensive complications were not a reason for exclusion from the study, but only 3 patients had evidence of target organ disease. One had a history of myocardial infarction, one had azotemia (serum creatinine, $\geq$1.5 mg/dl), and one had both azotemia and angina pectoris. None had accelerated hypertension (Keith-Wagener-Barker groups III and IV).

The plan and purpose of the investigation were explained to the patients, and each signed an informed consent form before being included in the study.

This study was supported by a grant from Bristol Laboratories, Syracuse, New York. Salutensin was furnished for this study by Bristol Laboratories.

All subjects had a history of hypertension; 16 were taking antihypertensive medication when selected, but discontinued therapy at least one month before entering the study.

Patients were seen in the office at two-week intervals throughout the study. Blood pressure was measured in the right arm with a standard mercury manometer; the 5th Korotkoff phase was used as the diastolic blood pressure. At each visit, after an initial 10-minute rest, three blood pressure recordings were taken at 5-minute intervals with the patient seated. The average of the three readings was taken as the blood pressure for each visit.

To qualify, each subject had to have an average diastolic blood pressure of >95 mm Hg on each of three consecutive office visits. Average diastolic blood pressure of ≥120 mm Hg on any visit disqualified the patient.

Before treatment with the reserpine/hydroflumethiazide combination was started, the ambulatory blood pressure monitor was applied and worn for 24 hours. A complete history and physical examination were obtained before starting therapy as were fasting blood glucose, serum uric acid, creatinine, and potassium as well as an electrocardiogram (ECG) and chest roentgenogram.

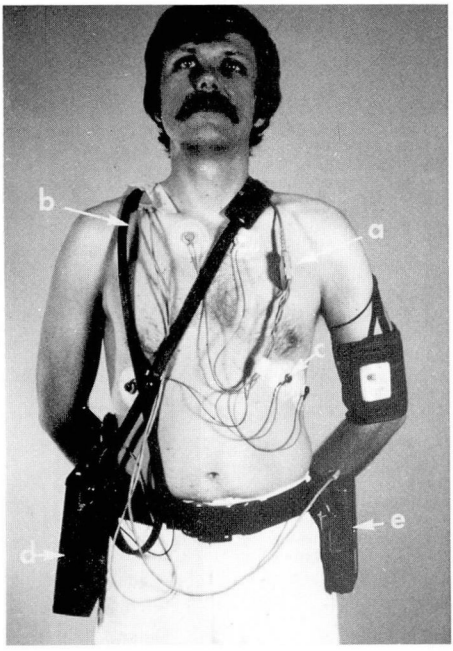
Therapy was started with one combination tablet of reserpine, 0.125 mg and hydroflumethiazide, 50 mg (Salutensin) once daily in the morning. Study endpoint was reached when average diastolic blood pressure was ≤90 mm Hg on each of two consecutive office visits. When this occurred, automated 24-hour blood pressure monitoring was repeated as were the determinations of serum uric acid, creatinine, potassium, and fasting blood glucose and ECG. The study drug was then discontinued.

If goal diastolic blood pressure had not been reached at the third office visit (six weeks), a second tablet of Salutensin was added to the regimen (two tablets were taken each morning). Whether or not goal blood pressure was reached by the end of the 12th week (six office visits), ambulatory blood pressure monitoring, blood tests, and ECG were repeated and the study drug was withdrawn. However, if the average diastolic blood pressure was ≤90 mm Hg for the first time on visit six, the study was extended for two more weeks before final monitoring of blood pressure, blood chemistry, and ECG was repeated.

A satisfactory office blood pressure response was defined as an average of ≤90 mm Hg diastolic on the last two consecutive office visits.

The automated ambulatory blood pressure monitor (Del Mar Avionics)[1-3] is based on Korotkoff sounds picked up by a microphone in a sphygmomanometer cuff, which is applied to the patient's nondominant arm and is automatically inflated by a compressor at predetermined intervals of 7.5, 15, or 30 minutes (*Figs. 1 and 2*). The Pressurometer II model also included simultaneous two-channel Holter recording of the ECG on magnetic tape along with the blood pressure readings. The magnetic tape is scanned by an electrocardioscanner. The resulting print-out includes premature beat counts, heart rate, ST-segment deviations and digital blood pressure recordings, as well as a graphic display of blood pressure.

The Pressurometer III model does not include simultaneous recording of the ECG although, as with the model II, ECG leads are attached so that the R wave can trigger deflation of the sphygmomanometer cuff. In model III the blood pressure data are stored in a solid state memory and transferred to an electrostatic printing system.



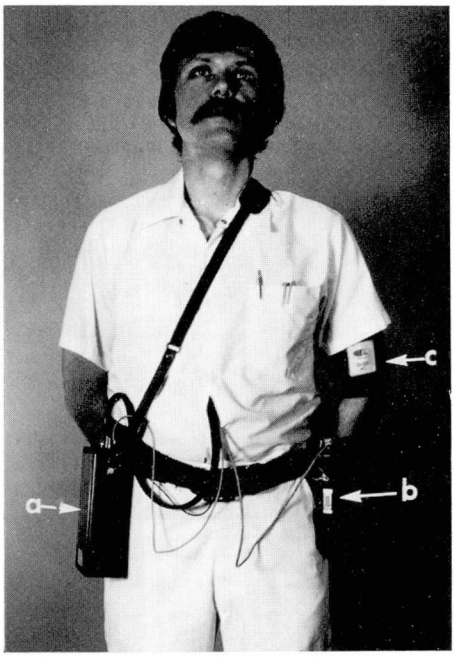


Fig. 1. The Del Mar Avionics Pressurometer II ambulatory blood pressure and ECG recording system on a subject. Components of the system are (a) ECG cable, (b) cuff inflation tubing, (c) ECG electrode, (d) pressurometer II, and (e) electrocardiocorder.

Fig. 2. The Del Mar Avionics Pressurometer II ambulatory blood pressure and ECG recording system on a fully dressed subject. Components of the system are (a) pressurometer II, (b) electrocardiocorder, (c) pressure cuff with transducer assembly under the cuff.

Intrapatient comparisons have shown a good correlation between determinations of blood pressure obtained by the Pressurometer and those obtained by the conventional auscultatory method[1, 2] as well as by direct arterial measurements.[1]

Auscultatory blood pressure measurements were made at the time of application and again at the time of removal of the automated blood pressure equipment to assure similar readings.

Technical problems with the automated equipment frequently necessitated repeating 24-hour recordings until at least 60% of the readings appeared valid.

Thirteen patients were monitored with the Pressurometer II and 4 were monitored with the Pressurometer III; 4 had pretherapy monitoring on Pressurometer II and post-therapy monitoring on Pressurometer III.

Thirty-five patients signed informed consent to participate in the study. Five were disqualified because the diastolic pressure did not average >95 mm Hg on three consecutive visits and one was disqualified because the diastolic pressure was ≥120 mm Hg. One woman could not tolerate wearing the automated blood pressure equipment and was excluded. Seven were disqualified for other reasons.

Results

Effect on office blood pressure

Sixteen patients had diastolic blood pressure of ≤90 mm Hg on each of their

Table 1. Salutensin study

	Pretreatment					Post-treatment				
			24-hour BP (mm Hg)					24-hour BP (mm Hg)		
Case	Variable	Last pretreatment office BP (mm Hg)	Mean ± SD	90% Range	% of time DBP ≥95	Variable	Last post-treatment office BP (mm Hg)	Mean ± SD	90% Range	% of time DBP ≥95
* 1	Systolic	157	139 ± 28	108–216	...	Systolic	131	136 ± 28	105–224	...
	Diastolic	105	97 ± 16	77–114	54	Diastolic	95	103 ± 52	77–117	70
2	Systolic	138	131 ± 23	101–162	...	Systolic	126	119 ± 29	95–218	...
	Diastolic	103	100 ± 15	79–121	72	Diastolic	87	90 ± 58	74–97	9
3	Systolic	143	142 ± 32	110–210	...	Systolic	139	138 ± 22	108–174	...
	Diastolic	103	85 ± 16	61–107	20	Diastolic	86	85 ± 15	63–106	28
4	Systolic	157	140 ± 17	116–165	...	Systolic	117	114 ± 17	91–130	...
	Diastolic	106	105 ± 12	88–124	82	Diastolic	80	89 ± 63	71–100	9
5	Systolic	139	123 ± 31	96–216	...	Systolic	143	113 ± 22	96–140	...
	Diastolic	110	93 ± 12	76–118	40	Diastolic	97	85 ± 12	75–102	13
6	Systolic	165	168 ± 58	134–227	...	Systolic	123	138 ± 36	91–226	...
	Diastolic	111	115 ± 25	93–159	93	Diastolic	77	96 ± 28	66–142	41
7	Systolic	160	151 ± 21	123–182	...	Systolic	137	137 ± 31	107–218	...
	Diastolic	100	110 ± 21	81–133	84	Diastolic	80	97 ± 24	69–122	53
8	Systolic	152	145 ± 21	111–176	...	Systolic	99	112 ± 33	87–220	...
	Diastolic	99	99 ± 22	75–118	59	Diastolic	67	87 ± 63	66–103	6
9	Systolic	178	183 ± 24	156–230	...	Systolic	160	151 ± 25	123–193	...
	Diastolic	111	127 ± 54	90–177	94	Diastolic	78	99 ± 61	74–120	41
* 10	Systolic	165	157 ± 32	109–204	...	Systolic	143	130 ± 23	104–172	...
	Diastolic	109	102 ± 25	75–170	57	Diastolic	89	74 ± 13	55–95	5
11	Systolic	150	147 ± 16	128–167	...	Systolic	143	125 ± 13	106–143	...
	Diastolic	102	96 ± 12	79–110	60	Diastolic	90	86 ± 14	66–103	20
12	Systolic	164	140 ± 33	91–195	...	Systolic	121	117 ± 24	81–149	...
	Diastolic	98	94 ± 62	59–122	39	Diastolic	81	82 ± 14	55–100	15
13	Systolic	140	155 ± 21	126–186	...	Systolic	126	132 ± 18	112–152	...
	Diastolic	96	85 ± 15	71–98	10	Diastolic	80	80 ± 20	65–89	4
* 14	Systolic	147	163 ± 22	128–193	...	Systolic	130	145 ± 25	115–201	...
	Diastolic	98	112 ± 21	86–138	86	Diastolic	80	92 ± 19	75–134	22
15	Systolic	173	138 ± 29	99–197	...	Systolic	128	120 ± 25	86–155	...

	Diastolic	100	97 ± 26	68–138	45	Diastolic	80	84 ± 23	58–116	20
16	Systolic	173	194 ± 26	165–237	...	Systolic	144	174 ± 17	145–200	...
	Diastolic	113	125 ± 19	102–150	99	Diastolic	87	105 ± 14	87–128	80
17	Systolic	152	136 ± 24	109–169	...	Systolic	116	116 ± 22	86–143	...
	Diastolic	103	91 ± 21	68–110	31	Diastolic	79	81 ± 17	58–102	14
* 18	Systolic	171	171 ± 15	151–196	...	Systolic	150	131 ± 13	110–153	
	Diastolic	110	116 ± 15	98–131	99	Diastolic	100	92 ± 11	77–102	43
* 19	Systolic	141	138 ± 21	116–177	...	Systolic	153	140 ± 18	114–162	...
	Diastolic	107	106 ± 15	91–122	90	Diastolic	110	99 ± 13	82–112	70
20	Systolic	160	129 ± 23	88–169	...	Systolic	108	123 ± 23	96–144	...
	Diastolic	96	80 ± 17	54–108	19	Diastolic	70	66 ± 24	47–91	4
21	Systolic	170	142 ± 19	109–167	...	Systolic	103	118 ± 27	85–148	...
	Diastolic	100	94 ± 18	65–118	52	Diastolic	70	77 ± 23	50–96	8

* 2 Salutensin tablets daily.
DBP = diastolic blood pressure.

last two office visits and were considered to demonstrate a satisfactory response to therapy. Fourteen of these were taking only one tablet daily and two required two tablets daily.

Five patients (cases 1, 3, 5, 18, and 19) (*Table 1*) did not achieve average office blood pressures ≤90 mm Hg for the last two visits. Three were taking two tablets daily. One could not tolerate two tablets daily because of side effects. Another stopped treatment after four weeks because of intolerable nasal stuffiness from reserpine (patient 3) (*Table 1*). At his last office visit before discontinuing treatment, his average diastolic blood pressure was 86 mm Hg, but because he did not have two consecutive office visits with diastolic blood pressure ≤90 mm Hg he was classified as an unsatisfactory responder.

Effect on ambulatory blood pressure

Figure 3 is a graphic display of three-reading rolling averages of blood pressure measured by the ambulatory blood pressure monitor on one of the patients in the study.

Office blood pressures and summaries of the 24-hour monitoring are presented for each patient both at pretreatment and post-treatment in *Table 1.* The central 90% range, and the mean and standard deviation of all systolic and diastolic blood pressures are presented. Percentage of time during the 24 hours that the diastolic blood pressure was ≥95 mm Hg, the arbitrary cutoff point, is indicated.

During the 24-hour blood pressure measurement, systolic pressure varied by as much as 135 mm Hg (all varied by at least 37 mm Hg) in the truncated range previously defined. Measurements of diastolic blood pressure varied by as much as 95 mm Hg, and all varied by at least 23 mm Hg.

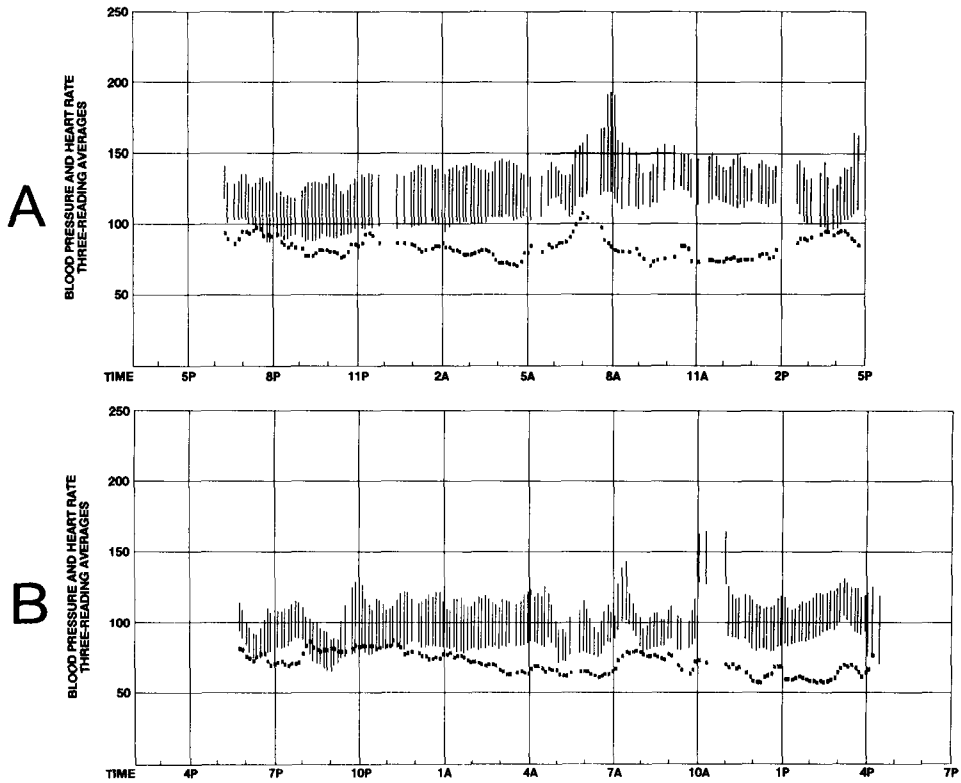


Fig. 3. Graphic display of 3-reading rolling averages of blood pressure and pulse rate as recorded by the Avionics Pressurometer in a 58-year-old male with primary hypertension, before (**A**) and at the end (**B**) of the period of treatment with reserpine, 0.125 mg and hydroflumethiazide, 50 mg (Salutensin) once daily.

Before treatment, correlation between the value of the office diastolic blood pressure and the diastolic blood pressure percentage ≥95 mm Hg was significant ($p < 0.01$). However, after treatment (Spearman) this correlation was only marginally significant ($p < 0.10$).

To consider the effect of treatment on diastolic blood pressure, attention is focused on the percentage of time during the 24-hour monitoring period that the diastolic blood pressure was ≥95 mm Hg. *Table 2* shows the mean and range of this percentage before and after treatment. Clearly, there is a significant effect from treatment ($p < 0.001$ by Wilcoxon signed rank test). In two patients (cases 1 and 3) the percentage actually increased with treatment. In one other patient (case 13) there was very little change in percentage. However, in the remaining 18 patients there were marked improvements (*Table 3*). For two patients (13 and 20) the percentage of time diastolic blood pressure exceeded 95 mm Hg before treatment was

Table 2. Percent of time diastolic blood pressure ≥95 mm Hg

Pretreatment	
Mean	61.2%*
Range	10%–99%
Post-treatment	
Mean	27.4%*
Range	4%–80%

* $p = <0.001$ by Wilcoxon signed rank test.

less than 20%. Finally, even though there were marked improvements with therapy for some patients, the percentage of time with high diastolic blood pressure post-treatment equaled or exceeded 40% for 7 patients (cases 1, 6, 7, 9, 16, 18, and 19). Five of these (cases 6, 7, 9, 16, and 18) responded satisfactorily with respect to office blood pressure readings (*Table 3*).

Mean values for systolic and diastolic blood pressures and pulse rate for each individual, pretherapy and post-therapy are shown in *Table 4*. For all 21 patients the average 24-hour blood pressure was reduced from 149 to 130 mm Hg systolic and from 105 to 88 mm Hg diastolic. The average pulse rate was reduced from 82 to 73 beats/min. All reductions were highly significant.

Table 3. Percent of time diastolic blood pressure ≥95 mm Hg

Post-treatment compared to pretreatment			Number of patients
Increased			2
Minimal decrease	<10%		1
Decreased	>10%		18
	≥25%	12	
	10%–25%	6	
Total			21

Average blood pressures were higher from 8 A.M. to 8 P.M. than from 8 P.M. to 8 A.M., both before and during therapy, but for both periods they were significantly lower during therapy than before. Treatment did not obliterate this diurnal difference. The standard deviations for systolic and diastolic blood pressure did not change significantly as a result of treatment (*Table 5*).

Side effects

At each visit, before and during the treatment period, symptoms volunteered by the patient were recorded on a special form and were classified as mild, moderate, or severe. At the end of the study an attempt was made to determine whether the symptoms were related to the drugs.

Five patients had side effects definitely attributed to one or both of the drugs contained in Salutensin (*Table 6*). Eight patients had no side effects attributable to the drugs and 11 patients had symptoms possibly drug related including 3 who also had side effects that could definitely be attributed to drugs (*Table 7*).

Two patients could not complete the protocol because of side effects. Both

Table 4. Individual mean values before and at the end of the treatment period

	Pretreatment			Post-treatment			
Period	Mean	SD	Range	Mean	SD	Range	p
24 Hour							
Systolic (mm Hg)	149	18	123–194	130	15	112–174	<.0001
Diastolic (mm Hg)	105	22	80–186	88	10	66–105	<.0001
Pulse rate (b/m)	82	16	58–119	73	14	57–116	<.0002
8 A.M.–8 P.M.							
Systolic (mm Hg)	154	20	127–203	134	16	114–177	<.0002
Diastolic (mm Hg)	105	12	80–129	91	10	68–104	<.0001
Pulse rate (b/m)	86	14	67–122	76	14	60–115	<.0001
8 P.M.–8 A.M.							
Systolic (mm Hg)	144	18	120–187	126	15	109–170	<.0001
Diastolic (mm Hg)	99	14	78–130	85	11	65–106	<.0002
Pulse rate (b/m)	79	16	56–118	69	14	52–107	<.0002

Table 5. Individual standard deviations before and at the end of treatment period

Period	Pretreatment Mean	Pretreatment Range	Post-treatment Mean	Post-treatment Range	p
24 hour					
Systolic (mm Hg)	26	15–58	23	13–36	0.14
Diastolic (mm Hg)	24	12–62	28	11–63	0.55
Pulse Rate (b/m)	15	8–30	13	7–27	0.03
8 A.M.–8 P.M.					
Systolic (mm Hg)	27	14–80	23	12–37	0.38
Diastolic (mm Hg)	23	7–86	25	8–92	0.79
Pulse rate (b/m)	13	7–40	13	7–38	0.69
8 P.M.–8 A.M.					
Systolic (mm Hg)	22	12–29	22	1–37	0.79
Diastolic (mm Hg)	21	8–93	22	7–80	0.44
Pulse rate (b/m)	14	6–30	11	4–29	0.02

Table 6. Side effects from reserpine and/or hydroflumethiazide (5 patients)

Side effects	No. of patients: Severity Mild	Moderate	Severe
Nasal congestion	0	1	2*
Dryness of mouth	1	2	0
Epigastric burning	0	1	0
Decreased energy level	0	1	0
Impotence	0	0	1

* Forced premature discontinuation of treatment in both.

Table 7. Side effects possibly related to reserpine and/or hydroflumethiazide (11 patients)*

Side effects	No. of patients: Severity Mild	Moderate	Severe
Nausea	0	1	0
Anorexia	1	0	0
Dryness of mouth	1	0	0
Paresthesia	3	0	0
Increased appetite	1	0	0
Mental depression	1	1	0
Headache	1	2	0
Impotence	1	0	0
Loss of libido	0	1	0
Pruritis	0	1	0
Aching and malaise	0	2	1
Edema	1	1	0
Diarrhea	1	0	1
Abdominal cramps	0	1	0
Dizziness	2	2	0
Constipation	1	0	0
Nightmares	1	0	0

* Includes 3 patients who also had side effects that could definitely be attributed to the drugs.

complained of severe nasal congestion and in addition one complained of generalized aching, malaise, and depression. The latter refused to take two tablets daily and his diastolic pressure did not fall to ≤90 mm Hg. The other patient refused to continue taking medication after four weeks even though his diastolic blood pressure was 86 mm Hg on the second office visit. These patients accounted for 2 of the 5 treatment failures based on office blood pressure.

No patient had a change in the ECG at the end of treatment.

The results of blood chemistry determinations before and at the end of the treatment period are summarized in *Table 8.* An unanticipated finding was a significantly lower average blood glucose at the end of the study than before treatment was started.

Although the average serum potassium was significantly lower at the end of treatment than it was before treatment, no patient had serum potassium <3.2 mEq/L at the end of the treatment

Table 8. Effect of treatment with reserpine/hydroflumethiazide on blood constituents

	Potassium (mEq/L)		Glucose (mg/dl)		Uric acid (mg/dl)		Creatinine (mg/dl)	
	Control	Rx	Control	Rx	Control	Rx	Control	Rx
Mean	4.2	3.8	105.8	91.2	6.6	7.1	1.1	1.1
SD	0.4	0.3	24.1	19.8	1.2	1.5	0.2	0.2
p*	<0.009		<0.006		<0.15		<0.35	

* Sign test.

period and none required potassium supplementation.

There were no significant changes in the concentrations of serum uric acid or serum creatinine as the result of treatment with the reserpinehydroflumethiazide combination.

Comment

Taking medication only once daily for a chronic disease such as hypertension is generally considered to be advantageous in enhancing compliance. Combinations of a long-acting adrenergic inhibiting drug such as reserpine with a diuretic in a single tablet offer this advantage.

In a study of 21 patients with mild to moderate hypertension, 16 had diastolic blood pressures in the office controlled (≤90 mm Hg) with one or two tablets of reserpine (0.125 mg) hydroflumethiazide (50 mg) combination taken once daily in the morning.

To estimate the control of blood pressure for these patients throughout a 24-hour period, an automated device was used to record blood pressure every 7.5 minutes. The percentage of time that the diastolic blood pressure was ≥95 mm Hg during the 24-hour period of monitoring was reduced from 61.2% before treatment to 27.4% at the end of treatment ($p < 0.001$). For 18 of 21 patients treatment produced >10% decrease in the percentage of time that diastolic readings were ≥95 mm Hg.

Although the averages of the 24-hour systolic and diastolic blood pressures were reduced significantly by the reserpine-hydroflumethiazide combination, the blood pressure variability was not greatly affected by antihypertensive therapy as indicated by the absence of significant change in standard deviations (*Table 5*). This was true during the 8 A.M. to 8 P.M. interval as well as during the 8 P.M. to 8 A.M. interval. Standard deviations were calculated by using *all* readings obtained in the 24-hour period, not just the central 90% range shown in *Table 1*.

Only 2 of 21 patients experienced side effects severe enough to require deviation from protocol. In both cases the side effect was nasal congestion. Eight patients had no side effects at all. Eight patients had symptoms that could not definitely be attributed to the drugs, 2 patients had side effects definitely drug related and 3 had both.

There were no clinically significant changes in serum potassium, serum creatinine or serum uric acid. Surprisingly, the average blood glucose concentration was lower at the end of the study than it was before treatment was started.

Use of the automated ambulatory blood pressure monitor to evaluate duration of effect of antihypertensive agents is relatively new. Priest et al[4] have reported results of this monitoring technique in one patient receiving captopril for management of resistant hy-

pertension. Garrett[5] has studied pindolol and hydrochlorothiazide using this method. Other studies of the duration of effect of antihypertensive agents are ongoing in other laboratories using this modality.

Continuous intra-arterial blood pressure recordings have been used to evaluate the duration of antihypertensive effect of some drugs,[6] but this is a complicated, invasive procedure with limited applicability.

Summary

A combination tablet containing reserpine, 0.125 mg, and hydroflumethiazide, 50 mg (Salutensin) taken once daily in the morning controlled office diastolic blood pressure in 16 of 21 patients with mild to moderate hypertension. Twenty-four hour blood pressure monitoring before and at the end of the treatment period revealed that the average percentage of diastolic blood pressure determinations ≥95 mm Hg decreased from 61.2 to 27.4 (*Table 1*) and by at least 10% for 18 of 21 patients.

Only 5 of 21 patients had side effects that could definitely be attributed to the drugs and in only 2 were these annoying enough to force a deviation from protocol.

Acknowledgment

The authors gratefully acknowledge the professional assistance of Betty Gurney, R.N., Mae Grice, L.P.N., Margaret Saunders, L.P.N., and Lee Williams, R.N. We also thank Veronica Hiebel for assistance in preparing the manuscript.

References

1. Harshfield GA, Pickering TG, Laragh JH: A validation study of the Del Mar Avionics ambulatory blood pressure system. Ambulatory Electrocardiology 1979; **1:** 7–12.
2. Sheps SG, Elveback LR, Close EL, Kleven MK, Bissen C: Evaluation of the Del Mar Avionics automatic ambulatory blood pressure-recording device. Mayo Clin Proc 1981; **56:** 740–743.
3. Pickering TG, Harshfield GA, Kleinert HD, Blank S, Laragh JH: Blood pressure during normal daily activities, sleep and exercise. Comparison of values in normal and hypertensive subjects. JAMA 1982; **247:** 992–996.
4. Priest RT, Weber MA, Brewer DD, Winer RL, Eltorai MI, Wyle FA: The use of ambulatory blood pressure monitoring to assess the antihypertensive efficacy of captopril (SQ 14,225) in a patient with treatment-resistant hypertension. Ambulatory Electrocardiology 1979; **1:** 1–16.
5. Garrett B: Pindolol and hydrochlorothiazide in essential hypertension. A three-way, double-blind, parallel study with 24-hour ambulatory blood pressure measurement (abst). Am J Cardiol 1982; **49:** 924.
6. Goldberg AD, Raftery EB: Patterns of blood-pressure during chronic administration of postganglionic sympathetic blocking drugs for hypertension. Lancet 1976; **2:** 1052–1054.