RENAL HEMODYNAMICS IN HYPERTENSIVE PATIENTS FOLLOWING ADMINISTRATION OF PENDIOMIDE

JOHN H. MOYER, M.D., ROBERT MCCONN, M.D., WITH THE TECHNICAL ASSISTANCE OF ALICE MILNER AND C. POLK SMITH

THE renal hemodynamic effects of blood pressure reduction with pendiomide administered by continuous intravenous infusion to normal individuals was described in a previous communication (1). The current report is a similar evaluation but the pendiomide was administered to patients with hypertension. Observations were made on renal hemodynamic responses and water and electrolyte excretion. These results were then compared with observations made on a similar group of patients who received hexamethonium or Arfonad,® D-3, 4(1, 3-dibenzyl-2-keto-imidizalido)-1,2-trimethylene thiophanium d-camphor sulfonate.

METHODS AND MATERIALS

Observations on renal function and on water and electrolyte excretion were made on 18 patients with hypertension. The ages ranged from 35 to 62 years. None of them had a history of primary renal disease. Glomerular filtration rate was measured by the inulin clearance technique and renal plasma flow was estimated by the clearance of para-aminohippurate. Blood pressure was measured by direct intra-arterial manometery. Arterial blood, which was collected through a manifold, was used for the chemical analyses. Methods and techniques have been described previously (2, 3, 4). Sodium and potassium excretion and the concentrations of these electrolytes in the plasma were determined using a Beckman flame photometer for analyses. All observations were made in the supine position.

After a period of equilibration, three successive ten-minute periods were obtained as control observations. The pendiomide was then administered by continuous intravenous infusion using a concentration of 1 to 2 mg. per cubic centimeter of 5 per cent glucose in distilled water. The rate of infusion was adjusted depending on the blood pressure response. The initial reduction in blood pressure was usually observed after 5 to 10 mg. of pendiomide were administered. After hemodynamic stabilization occurred, a "floor" in the blood pressure was obtained beyond which it was difficult to lower pressure. Only with a very rapid infusion was it possible to obtain an additional depression in blood pressure and this was usually limited to a reduction of 10 to

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20 mm. of mercury. After the initial induction period, the drug was administered at a rate of 1 to 5 mg. per minute. The maximum amount of pendiomide which was given was 800 mg. over a four hour period. The average was 325 mg. during a period of three hours. Observations were made for successive ten minute periods during the period of drug infusion, which lasted for three hours or more. Then norepinephrine was administered to these patients by continuous intravenous infusion and the blood pressure was increased so as to approximate the control levels. The infusion of pendiomide was continued at the same rate (concurrently with the norepinephrine infusion) as during the period of hypotension in order to maintain the same degree of ganglionic blockade. After the blood pressure was stabilized at approximately the control levels with norepinephrine, two successive ten-minute collection periods were obtained. Glomerular filtration rate, renal blood flow and excretion rates of water and electrolytes were determined similarly to the observations which were obtained during the period of maximum reduction in blood pressure with pendiomide.

RESULTS

The effects of pendiomide on mean blood pressure and on renal hemodynamics are summarized in table 1. During the first thirty minutes of pendiomide infusion, there was a significant reduction in mean blood pressure from 155 mm. of Hg for the group to 122 mm. Two hours after starting the infusion, the blood pressure decreased to 95 mm. Hg and a greater reduction in pressure was not observed with more prolonged drug administration. Associated with the initial reduction in mean blood pressure, there was a sharp decrease in renal blood flow ($p < 0.01$). However, after three hours of hypotension, the renal blood flow returned to or approximated the control observations in many of the patients ($p < 0.10$ for the group). Associated with the reduction in blood pressure there was a significant and maintained reduction in glomerular filtration rate ($p < 0.001$). There was no apparent tendency for the glomerular filtration rate to compensate by returning to control values. This reduction in glomerular filtration rate was associated with a marked and persistent reduction in urine volume ($p < 0.001$) and sodium excretion ($p < 0.001$). The potassium excretion showed a tendency to be reduced, but at no time was the reduction in potassium excretion statistically significant (table 2).

When norepinephrine was administered to the patients after three hours of continuous blood pressure reduction and the pressure increased to approximately control levels, there was a sharp increase in glomerular filtration rate as compared to period D_4 ($p < 0.001$). This was associated with an increase in urine volume and sodium excretion ($p < 0.01$). Although the urine volume showed an increase, it did not return to control values but remained significantly depressed ($p <$

TABLE 1

RENAL HEMODYNAMIC RESPONSE TO PENDIOMIDE

Patient	Mean Blood Pressure mm. Hg						Glomerular Filtration Rate ml./min.						Renal Blood Flow ml./min.						Renal Vascular Resistance*					
	C	D_1	D_3	D_2	D_4	NE	C	D_1	D_2	D_3	D_4	NE	C	D_1	D_2	D_3	D_4	NE	C	D_1	D_3	D_2	D_4	NE
1 A. D.	131	106	101	79	78	133	49	35	40	31	37	43	347	310	326	246	308	322	.38	.34	.31	.32	.25	.41
2 A. S.	142	132	122	99	89	—	116	86	92	84	102	—	1165	722	842	834	893	—	.12	.18	.14	.12	.10	—
3 O. F.	107	121	102	85	128	—	36	23	20	18	28	—	330	179	184	198	382	—	.51	.68	.55	.43	.34	—
4 A. C.	164	137	131	100	89	157	49	31	28	27	30	54	324	263	222	300	331	355	.51	.52	.59	.35	.27	.44
5 M. W.	151	125	83	71	95	121	60	56	30	32	72	63	518	557	354	457	704	786	.28	.22	.23	.16	.14	.15
6 R. M.	172	147	141	115	103	167	12	11	9	9	8	5	42	33	23	24	26	16	4.10	4.45	6.13	4.79	3.96	10.44
7 L. B.	173	94	139	128	102	148	78	18	40	23	21	73	758	500	559	394	922	900	.23	.19	.25	.32	.11	.16
8 A. H.	152	128	110	89	80	—	85	77	42	50	43	—	834	813	508	811	585	—	.18	.16	.22	.11	.14	—
9 M. S.	159	135	126	90	96	147	92	73	69	50	68	103	825	654	729	501	771	851	.19	.21	.17	.16	.12	.17
10 M. B. T.	148	111	101	118	120	157	134	84	95	124	126	163	1022	550	860	812	771	1295	.14	.20	.12	.15	.16	.12
11 S. T.	197	167	116	95	88	167	84	72	51	54	41	73	489	381	316	430	414	633	.40	.44	.37	.22	.21	.26
12 J. D.	149	127	104	84	88	121	61	55	49	48	42	43	458	465	415	483	492	488	.33	.27	.25	.17	.18	.25
13 W. L.	114	90	74	70	68	116	142	122	110	110	86	127	963	884	959	931	758	800	.12	.10	.08	.08	.09	.15
14 I. R.	140	106	117	101	99	141	149	146	143	127	110	156	1240	1317	1127	1016	954	929	.11	.08	.10	.10	.10	.15
15 E. W.	161	127	126	106	103	160	90	76	94	69	70	109	730	600	750	585	662	751	.22	.21	.17	.18	.16	.21
16 J. H.	166	142	126	99	95	136	113	117	91	93	90	94	789	896	713	870	946	695	.21	.16	.18	.11	.10	.20
17 E. H.	169	95	101	105	105	138	85	43	47	62	45	108	561	341	462	605	552	943	.30	.28	.22	.17	.19	.15
18 W.	128	112	94	74	84	—	122	98	109	107	111	—	1537	882	750	1203	1181	—	.08	.13	.13	.06	.07	—
Mean	155	122	112	93	95	144	87	68	64	62	63	87	720	575	561	598	647	697	.47	.40	.57	.44	.37	.95
% of Control		79	72	61	61	93		78	74	71	72	100		80	78	83	90	97		104	121	94	79	202
P Value <† P Value <‡‡		.001	.001	.001	.001	.01 .001‡‡		.001	.001	.001	.001	NS .001‡‡		.01	.01	.01	.10	NS NS‡‡		NS	NS	NS	.001	NS NS‡‡

Key to Table: C = Control observations—average of 3-10 minute periods.
D_1 = First 30 minutes after infusion of pendiomide started—average of 3-10 minute periods.
D_2 = One hour after infusion of pendiomide—average of 2-10 minute periods.
D_3 = Two hours after infusion of pendiomide—average of 2-10 minute periods.
D_4 = Three hours after infusion of pendiomide—average of 2-10 minute periods.
NS—P value >0.30.

* Renal vascular resistance = $\frac{\text{Mean blood pressure}}{\text{Renal blood flow}}$.

† $t = \bar{x}\sqrt{\frac{n(n-1)}{\Sigma s^2}}$ — using control value for comparison.

‡‡ Using Period D_4 for comparison.

TABLE 2

VITAL STATISTICS, SIDE EFFECTS, AND THE EFFECT OF PENDIOMIDE ON WATER AND ELECTROLYTE EXCRETION

Patient	Urine Volume cc./min.						Sodium Excretion μEq./min.						Potassium Excretion μEq./min.						Hematocrit				Age	Sex		Race		Side Effects
	C	D_1	D_2	D_3	D_4	NE	C	D_1	D_2	D_3	D_4	NE	C	D_1	D_2	D_3	D_4	NE	C	D_2	D_4	NE		M	F	C	W	
1 A. D.	8.4	1.9	1.2	1.4	1.2	1.5	320	176	187	157	158	207	22	18	22	18	27	27	28	26	26	24	49		1	1		Complained of backache
2 A. S.	10.7	5.5	1.2	0.9	0.3	—	424	212	141	114	38	—	49	34	36	34	39	—	48	41	41	—	54		1	1		None
3 O. F.	7.2	0.5	0.7	0.9	1.3	—	260	98	72	65	108	—	27	29	32	33	44	—	43	42	43	—	50		1	1		None
4 A. C.	7.7	2.9	1.5	0.8	0.8	3.1	298	70	69	32	19	399	95	66	54	64	92	156	38	35	35	36	43		1	1		Fatigue, nervous, "jittery"
5 M. W.	4.2	2.2	0.3	0.5	1.2	2.3	312	154	43	43	276	416	70	66	45	64	100	85	42	44	42	42	51		1	1		Somnolence
6 R. M.	2.5	1.9	1.3	1.2	1.0	0.3	283	154	91	66	49	148	26	29	26	31	27	8	33	26	24	24	41	1		1		None
7 L. B.	6.3	0.7	0.3	1.0	1.2	3.5	229	14	26	17	43	215	48	46	55	41	54	103	52	51	50	50	42		1	1		Nausea and vomiting
8 A. H.	2.6	0.7	0.3	0.2	0.1	—	498	152	56	36	17	—	30	23	27	31	30	—	38	35	35	—	58			1	1	Restless and chilly
9 M. S.	8.0	8.0	0.9	0.5	0.6	2.5	366	114	43	21	28	100	61	48	59	41	60	94	35	37	32	32	59		1	1		Fatigue, nausea, anxious
10 M. B. T.	10.6	0.9	0.6	0.6	0.4	3.9	157	15	10	35	14	464	64	31	47	33	22	125	41	40	41	39	40		1			Fatigue, slight shortness breath
11 S. T.	3.0	0.6	0.6	0.3	0.4	0.4	706	124	62	22	15	102	41	16	15	26	25	58	45	42	44	43	53	1		1		Anxious, restless
12 J. D.	11.0	7.5	1.6	0.8	1.0	1.4	430	119	98	53	62	64	36	27	17	43	37	36	36	35	35	35	50		1	1		Chest pain, nervous, shortness breath
13 W. L.	8.2	0.6	0.3	0.6	0.4	0.4	106	67	49	43	40	43	27	31	26	32	24	32	44	41	41	42	51	1		1		Restless, chilly, tremor
14 I. R.	9.9	0.5	0.7	0.6	0.6	1.1	330	57	93	44	44	420	40	50	40	36	32	59	46	46	44	45	47		1			None
15 E. W.	4.3	1.4	1.3	2.7	1.8	8.5	164	81	39	39	34	668	40	37	21	36	38	78	34	29	29	30	35		1	1		None
16 J. H.	5.4	1.1	0.7	0.2	0.6	1.4	551	176	73	44	35	176	49	79	33	45	51	60	45	44	43	44	62	1		1		None
17 E. H.	4.8	0.4	0.6	0.4	0.2	2.0	613	53	59	84	35	271	30	34	40	62	16	94	41	37	37	37	36		1			Urge to defecate
18 C. W.	2.5	1.7	0.5	0.6	0.6	—	312	154	43	43	276	—	76	66	45	63	100	—	40	36	36	—	48		1		1	Nausea
Mean	6.6	2.1	0.8	0.8	0.8	2.3	353	111	70	53	72	264	47	41	36	41	45	73	41	38	38	37	48					
% of Control		32	12	12	12	35		31	20	15	20	75		87	77	87	96	155		93	93	90						
P Value <		.001	.001	.001	.001	.001		.001	.001	.001	.001	NS		.20	.10	.20	NS	.01		.001	.001	.001						
P Value <‡‡						.01‡‡						.01‡‡						.01‡‡				NS‡‡					
Mean Value for Plasma Concentration							136	141	141	140	139	133	4.7	4.7	4.6	4.5	4.2	4.2										
P Value <								NS	NS	.20	.05	.20		NS	NS	.10	.001	.01										

Key to table: C–D_4—see Table 1 for key to abbreviations.
‡‡ Using Period D_4 for comparison.

0.001) despite the fact that glomerular filtration rate returned to control levels. When norepinephrine was given, the potassium excretion increased markedly and even exceeded the control values ($p < 0.01$).

DISCUSSION

These observations indicate that the renal responses to blood pressure reduction with pendiomide in the hypertensive patients were qualitatively similar to the responses of normotensive individuals. However, the degree of alteration was more marked in the hypertensive patients. Moreover, the alterations in renal function in the hypertensive patients occurred within a normotensive blood pressure range. A comparison of hypertensive patients with normotensive subjects receiving pendiomide, hexamethonium or Arfonad® is summarized in table 3. It would appear that in the normotensive subjects, there are no essential differences among the three ganglionic blocking agents except the degree of blood pressure reduction; the greater the blood pressure reduction, the more marked the renal response. Since Arfonad® produced a greater reduction in blood pressure than pendiomide and hexamethonium, there was a correspondingly greater reduction in glomerular filtration rate and renal blood flow which persisted throughout the period of drug infusion. The effect on renal vascular resistance was not statistically significant for any of the drugs studied. Arfonad® was the only one of the three agents in which renal vascular resistance tended to increase, again a reflection of the greater degree of blood pressure reduction.

In contrast to the normotensive subjects, the mean blood pressure in the hypertensive patients was reduced to about the same level with pendiomide, hexamethonium or Arfonad® and was within the normotensive range with all three agents (95, 99 and 91 mm. of Hg respectively). This was associated with a reduction in glomerular filtration rate, and sodium and water excretion. There was an initial reduction in renal blood flow when all of the agents were administered to the hypertensive patients. This tended to return to or toward the control levels as the infusion was continued. Renal vascular resistance decreased significantly after prolonged infusion with both Arfonad® and pendiomide, but this did not occur with hexamethonium. The significance of this, if any, is not apparent.

It seems well worth noting the effect on water and electrolyte excretion in patients who are receiving ganglionic blocking agents by continuous infusion for controlling blood pressure during surgery. With the marked reduction in water and sodium excretion, as exhibited in these experiments, it would appear that it is quite possible to overhydrate the patient and thus precipitate acute congestive heart failure. The response to norepinephrine is of significance in that it indicates that the renal hemodynamic alterations are a direct result of the hypotension rather than being related to a specific ganglionic blocking agent.

TABLE 3

COMPARISON OF RENAL HEMODYNAMICS RESPONSES TO PENDIOMIDE, HEXAMETHONIUM, AND ARFONAD® IN NORMOTENSIVE AND HYPERTENSIVE PATIENTS

	Mean Blood Pressure mm. Hg			Glomerular Filtration Rate ml./min.			Renal Blood Flow ml./min.			Renal Vascular Resistance			Urine Volume ml./min.			Sodium Excretion mEq./min.			Number Patients Studied
	C	H	2H	C	H	2H	C	H	2H	C	H	2H	C	H	2H	C	H	2H	
Normotensive Patients																			
Pendiomide	97	83	71	134	110	115	1309	1116	1199	.08	.12	.07	9.3	4.9	1.8	162	146	68	9
P Value*	—	.01	.01	—	.20	.10	—	NS	.30	—	NS	.20	—	.05	.01	—	NS	.01	
Arfonad®	98	81	57	121	96	64	1143	774	504	.09	.10	.15	3.9	3.2	0.7	161	115	48	9
P Value*	—	.02	.01	—	.02	.01	—	.02	.01	—	NS	.30	—	NS	.01	—	.10	.01	
Hexamethonium	98	68	64	113	92	93	1108	874	1007	.10	.11	.07	3.1	1.4	0.6	105	25	21	9
P Value*	—	.01	.01	—	.01	.02	—	.20	.30	—	NS	.10	—	.20	.05	—	.01	.01	
Hypertensive Patients																			
Pendiomide	155	122	95‡	87	68	63‡	720	575	647‡	.47	.49	.37‡	6.6	2.1	0.8‡	353	111	72‡	18
P Value*	—	.001	.001	—	.001	.001	—	.01	.10	—	NS	.001	—	.001	.001	—	.001	.001	
Arfonad	143	124	91	88	72	66	690	600	858	.24	.26	.17	7.7	4.5	1.1	352	199	96	8
P Value*	—	.01	.01	—	.01	.02	—	.02	.30	—	NS	.02	—	.02	.01	—	.02	.01	
Hexamethonium	132	111	99‡	76	46	51‡	750	452	526‡	.21	.27	.22‡	7.1	3.6	0.6‡	274	179	64‡	8
P Value*	—	.01	.001	—	.01	.01	—	.05	.05	—	.30	NS	—	.01	.01	—	.001	.01	

C = Control.
H = Initial period of hypotension.
2H = Observations after hypotension for 2 hours (or more see ‡).
* = P value recorded only when less than 0.30—when greater than this it is recorded as NS.
‡ = Observations made after blood pressure reduction for 3 hours.

In addition, when excessive hypotension occurs, norepinephrine is an effective antidote. When the blood pressure is raised with this agent, glomerular filtration rate and the excretion rates of water and electrolytes are increased.

SUMMARY AND CONCLUSIONS

The renal hemodynamic effects of blood pressure reduction with pendiomide in patients with hypertension have been studied. As the blood pressure is reduced to normotensive levels, renal blood flow and glomerular filtration rate are depressed. With maintained blood pressure reduction for three hours or more, renal blood flow tends to return toward the control levels, whereas glomerular filtration rate remains depressed and shows no tendency to increase.

Associated with the reduction in glomerular filtration rate there is a marked and maintained reduction in the excretion rates of water and sodium. These excretion rates remain depressed as long as the infusion of pendiomide is continued and the blood pressure is reduced.

There are minor differences between the renal hemodynamic responses to pendiomide as compared to hexamethonium and Arfonad.® These differences have been discussed.

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