The Effect of 3-Aminophthalhydrazide on Diuresis and Blood Pressure in Dogs (34910)

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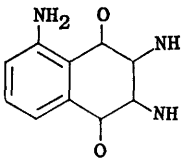
3-Aminophthalhydrazide was first synthesized by Schmitz (1) in 1902. Its chemical structure is as follows:



3-Aminophthalhydrazide

This substance is only slightly soluble in water and organic solvents, but freely soluble in acid and alkali. It fluoresces strongly in neutral and weak acid solution and emits luminescence when an oxidizing agent is added to it in alkaline solution. The substance is unstable when exposed to light, but is comparatively thermostable. It has been suggested that 3-aminophthalhydrazide with its γ, β-unsaturated ketones may have a metabolic function as an oxidation–reduction catalyst and exhibit wide biological activity, some of which has been reported previously (2–5). In the experiments reported here 3-aminophthalhydrazide was administered to dogs and the effects on diuresis and blood pressure were recorded.

Methods. The methods in these experiments were similar to those of Moyer and Handley (6). Five female dogs, ranging in weight from 13 to 19 kg, were used. The dogs were hydrated by administration of 40 ml/kg of water by mouth. Forty-five min later they were anesthetized with pentobarbital, 30 mg/kg of body weight, given intravenously. Creatinine infusion was used to measure glomerular filtration rate (GFR) and para-aminohippurate (PAH) infusion to estimate renal plasma flow (RPF). The plasma concentration range maintained for creatinine was 20 to 50 mg/100 ml, and for para-aminohippurate (PAH), 1 to 2 mg/100 ml. A priming dose of these substrances containing 50 mg/kg of creatinine, and 5 mg/kg of PAH was administered followed by a constant intravenous infusion using a sigmamotor. The infusion solution contained 8 mg of creatinine and 1 mg of PAH/100 ml, and was administered at the rate of 2 to 5 ml/min, depending on the size of the dog, so as to maintain a constant blood concentration of creatinine and PAH. At least 30 min were allowed for equilibration following the priming infusion before the control observations were started. Cadmium sulfate filtrates were used for analysis. The methods of Bonsnes and Taussky (7) and Smith and his associates (8) were used for the creatinine and PAH determinations, respectively.

Mean blood pressure was measured by a damped mercury manometer connected through a manifold to an indwelling arterial needle. Arterial blood, collected in heparinized syringes, was used for chemical analysis. Urine was collected at 10-min intervals from a catheter previously inserted into the ureter. After two successive 10-min control periods, 2.5 mg of 3-aminophthalhydrazide was administered intravenously. Each animal, therefore, served as its own control. The specimens of blood and urine were collected during two successive 10-min periods, beginning 5 min after administration of the 3-aminophthalhydrazide and then 1 and 2 hr after the injection of the drug.

Results. The effect of 3-aminophthalhydrazide on urine volume and electrolytes is

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TABLE I. Effect of 3-Aminophthalhydrazide on Water and Electrolyte Excretion.[a]

Dog no.	Wt (kg)	Urine vol (ml/min)				Plasma sodium (meq/liter)				Plasma potassium (meq/liter)				Sodium excretion (meq/min)				Potassium excretion (meq/min)			
		C	D_1	D_2	D_3	C	D_1	D_2	D_3	C	D_1	D_2	D_3	C	D_1	D_2	D_3	C	D_1	D_2	D_3
1	18.5	6.8	8.6	15.0	7.8	147	141	134	132	4.07	4.23	3.67	3.67	0.15	0.16	0.28	0.15	0.04	0.04	0.07	0.04
2	13	7.5	12.5	14.3	10.8	143	138	133	128	3.72	3.96	3.62	3.65	0.04	0.11	0.15	0.15	0.03	0.05	0.04	0.04
3	19	8.1	7.5	12.5	12.8	138	135	131	136	3.60	3.66	3.69	3.76	0.04	0.04	0.15	0.12	0.03	0.05	0.04	0.04
4	15	7.2	8.2	10.4	8.4	144	136	135	132	3.36	3.24	3.10	3.14	0.05	0.07	0.09	0.07	0.03	0.04	0.02	0.02
5	17	3.9	3.7	4.0	2.8	137	136	135	133	2.97	2.80	2.74	2.79	0.04	0.05	0.05	0.07	0.03	0.02	0.02	0.03
Mean	16.5	6.7	8.1	11.2[c]	8.5	142	137[d]	134[d]	132[d]	3.54	3.58	3.36	3.40	0.06	0.09	0.14[d]	0.11[c]	0.03	0.04	0.04	0.03
% of control[b]			120	168[c]	127		97[d]	94[d]	93[d]		101	95	96		150	233[d]	183[c]		133	133	100

[a] Abbrev.: C = control; D_1 = average of two 10-min periods started 5 min after 3-aminophthalhydrazide was given iv; D_2 = average of two 10-min periods taken 50 to 70 min after 3-aminophthalhydrazide was administered; D_3 = average of two 10-min periods taken 110 to 130 min after 3-aminophthalhydrazide was administered.

[b] Average postdrug value divided by average control value.

[c] $p < 0.05$; [d] $p < 0.01$.

TABLE II. Effect of 3-Aminophthalhydrazide on Mean Blood Pressure, Glomerular Filtration Rate, and Renal Plasma Flow.[a]

Dog no.	Mean blood pressure (mm Hg)				Glomerular filtration rate (ml/min)				Renal plasma flow (ml/min)				Filtration fraction				Hematocrit				Renal blood flow (ml/min)[b]			
	C	D_1	D_2	D_3	C	D_1	D_2	D_3	C	D_1	D_2	D_3	C	D_1	D_2	D_3	C	D_1	D_2	D_3	C	D_1	D_2	D_3
1	135	133	130	116	53	69	84	56	134	151	167	145	0.40	0.46	0.50	0.39	45	39	36	36	244	248	261	227
2	122	116	108	120	55	54	68	56	154	170	185	170	0.36	0.32	0.37	0.33	52	50	49	52	321	340	363	354
3	130	118	113	108	47	47	62	62	155	156	184	186	0.30	0.30	0.34	0.33	49	48	45	43	304	300	335	326
4	138	133	137	155	43	47	53	48	143	147	158	144	0.30	0.32	0.34	0.33	45	46	49	46	260	272	310	267
5	130	134	125	133	40	38	42	36	124	125	144	126	0.32	0.30	0.29	0.29	48	49	47	44	238	245	272	225
Mean	131	127	123[d]	126	48	51	62[d]	52	142	150	168[e]	154	0.34	0.34	0.37	0.33	48	46	45	44	273	281	308[e]	280
% of control[c]	97	94[d]	96		106	129[d]	108		106	118[e]	108		100	109	97		96	94	92		103	113[e]	103	

[a] Abbrev.: C = control; D_1 = average of two 10-min periods started 5 min after 3-aminophthalhydrazide was given iv; D_2 = average of two 10-min periods taken 50 to 70 min after 3-aminophthalhydrazide was administered; D_3 = average of two 10-min periods taken 110 to 130 min after 3-aminophthalhydrazide was administered.

[b] Renal blood flow = renal plasma flow/(1—hematocrit).

[c] Average postdrug value divided by average control value.

[d] $p < 0.05$; [e] $p < 0.01$.

presented in Table I. Urine volume was increased significantly 1 hr after the administration of the drug. Urinary sodium excretion was also increased significantly and reached maximum levels 1 hr after the injection. The increase in urinary potassium excretion was not significant. Plasma sodium levels were reduced significantly and did not return toward the control values in most of the dogs during the 2 hr of postinjection observation. The decrease in plasma potassium levels was not significant.

The renal hemodynamic response to 3-aminophthalhydrazide is presented in Table II. There was no significant variation between the two control periods. Although the blood pressure was significantly decreased 1 hr after administering 3-aminophthalhydrazide, both renal plasma and blood flow and GFR were increased, but tended to return toward the control levels in most of the dogs after this period of time. The filtration fraction remained relatively unchanged. The mean blood pressure also tended to return toward the control levels in most of the animals. There was a slight but insignificant reduction in the hematocrit associated with the depression in blood pressure.

Discussion. Following the intravenous administration of a single dose of 3-aminophthalhydrazide there was an increase in urine volume. This was associated with an increase in renal plasma and blood flow and glomerular filtration rate which became maximal 1 hr after administration of the drug. The increase in diuresis induced by 3-aminophthalhydrazide, therefore, appears to be caused by renal vasodilatation. Although the filtration fraction remained unchanged, the question of whether there was also an effect on tubular transport can only be clarified by additional experiments.

The drug also produced a decrease in plasma sodium together with an increase in the urinary excretion of this cation. The decreased sodium in the plasma was therefore produced by the renal hemodynamic changes rather than by the dilutional effect of prolonged water administration. The results with reference to potassium were in the same direction as sodium but inconclusive because they were not significant. The question of whether the drug also produced a change in tubular function with respect to electrolyte excretion must again await further experimental evaluation.

The mechanism by which 3-aminophthalhydrazide reduces blood pressure is also still unclear. In these experiments, however, the reduction of blood pressure was accompanied by an increase in urine volume, glomerular filtration rate, and renal plasma and blood flow. It therefore seems likely that the decrease in blood pressure was produced largely by a decrease in peripheral resistance.

Summary. 3-Aminophthalhydrazide given iv to five dogs decreased the systemic arterial blood pressure and produced a water diuresis together with increased natriuresis.

The results suggest that the chief effect of the drug is hemodynamic and related to renal as well as systemic vasodilatation. The possibility of an additional effect on renal tubular function, however, could not be excluded.

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