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Research Article

GUANIDINE EXCRETION IN RELATION TO HYPERTENSION

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A series of observations have been made recently, the results of which suggest, a relationship between arterial hypertension and guanidine metabolism. Major and Stephenson (1) studying the influence of certain urinary constituents on blood pressure, noted that methyl guanidine, a product of normal metabolism and a constituent of normal urine, had marked pressor effects. These authors suggested that this compound, if produced in excess or imperfectly excreted, might account for increased blood pressure. Creatinine and creatine, substances closely allied to methyl guanidine chemically, were found inert. Later (2) observations confirmed the rise in blood pressure following experimental injection of methyl guanidine. In addition it was then noted that, in short period experiments, rise in blood pressure produced by guanidine compounds could be abolished by the use of calcium or potassium chloride. The latter is of interest, in view of the clinical results obtained from the use of these salts as reported by Addison (3) and Addison and Clark (4), who found that these inorganic salts, when given in large doses (about 15 grams per day) over long periods of time, produced a diuresis and accompanying this there was a decided and prolonged fall in blood pressure in a large percentage of cases of hypertension. In a further communication Major (5) reported two cases of arterial hypertension in which the daily excretions of guanidine bases were observed. In both, during produced diuresis, a rise in urinary excretion of dimethyl-guanidine was accompanied by a fall in blood pressure. Experimental evidence was also presented by the same worker (6) favoring the view that the elevation in blood pressure

following administration of guanidine compounds is due to the peripheral constriction of the arterioles.

In view of the above findings we have made a study of the excretion of guanidine compounds in a series of normal individuals and in patients with hypertension.

In all their investigations Major and his co-workers employed the technical method described by Findlay and Sharpe (7) for the quantitative estimation of dimethylguanidine. In our earlier work with this technique some difficulty was encountered in that, in spite of the theoretical differences in solubility between guanidine picrate and the creatinine compound, the latter was found to interfere greatly with quantitative results. The method employed, subsequently, was that more recently described by Sharpe (8). The steps suggested by Sharpe for the separation of creatinine from guanidine (fractional crystallization or the use of blood charcoal) have yielded results sufficiently quantitative for the present purpose. By this method Sharpe has shown that about 90 per cent of added guanidine hydrochloride can be recovered from a solution containing this compound, sodium chloride, potassium chloride and creatinine hydrochloride. The same percentage recovery may also be noted when guanidine hydrochloride is added to normal urine. The writers are indebted to Dr. Sharpe for the helpful suggestions made in a personal communication, with reference to this method.

Observations were made first upon a series of normal urines. As noted by Major, marked fluctuations were found in the amounts excreted daily by the same individuals. Two possible explanations for this are suggested. Like most of the other nitrogenous substances excreted, the daily amounts may vary. In view, however, of the constancy of creatinine excretion and the chemical relationship between creatinine and methyl guanidine, it is quite possible that the total amount of guanidine bases excreted daily is constant for the individual, but that the relative proportions of the different compounds vary and that all of these are not recovered quantitatively by the method employed. In view of the above consideration data were collected to determine the average daily excretions in normal individuals. In each case observations were made on three successive days. The results on ten such individuals are recorded in table 1.

TABLE 1

Daily excretion of dimethyl guanidine by normal individuals

Subject	Day 1	Day 2	Day 3	Average per day
	mgm.	*mgm.*	*mgm.*	*mgm.*
1	174	84	112	123
2	68	127	148	114
3	132	186	147	155
4	88	147	82	106
5	147	132	78	119
6	66	43	117	75
7	142	176	164	160
8	58	124	86	89
9	94	178	98	123
10	162	141	67	123
Average				119

TABLE 2

Subjects with marked arterial hypertension

Hospital number	Age	Blood		Urine urea concentration			Blood pressure		Daily excretion of dimethyl-guanidine					
		Urea-N	Creatinine	First hour	Second hour	Urea concentration factor	Systolic	Diastolic	Day 1	Day 2	Day 3	Average per day	Albumin	Casts
		mgm. per 100 cc.	*mgm. per 100 cc.*	*per cent*	*per cent*				*mgm.*	*mgm.*	*mgm.*	*mgm.*		
4742	35	14	1.20	1.51	0.84	16	250	160	74	45	82	67	+	+
4878	42	39	1.60				145	100	214	110	78	134	0	0
4890	62	18	1.46	1.16	1.29	22	180	100	126	164	213	167	0	0
4944	48	17	1.47	1.14	1.62	32	210	110	68	111	46	75	+	+
4997	41	17	1.36	2.70	2.66	50	150	100	212	314	178	235	0	0
5004	76	24	1.70				180	90	174	80	96	117	+	+
5032	49	22	1.76				242	142	74	32	68	58	+	+
5095	55	39	2.02	1.33	1.40	13	200	128	112	47	84	81	+	+
5139	37	15	1.36	2.88	2.88	60	200	100	46	86	114	82	0	0
5194	56	98	4.68	1.16	1.11	4	270	165	84	38	56	59	+	+
5221	57	35	2.14	1.08	1.26	14	210	130	46	87	69	67	+	
5400	55	17	1.42	3.36	3.60	70	196	100	210	116	84	137	+	
6159	62	21	1.66	1.88	1.92	32	200	110	116	84	68	89	0	0
Average												105		

In table 2 are shown the average daily excretions in thirteen cases of marked arterial hypertension. In each case are also recorded, in order, the values of the blood urea nitrogen, blood creatinine, urine urea concentration following ingestion of 15 grams urea, and the urea concentration factor $\left(\frac{\text{mgm. Urea N per 100 cc. urine}}{\text{mgm. Urea N per 100 cc. blood}}\right)$, the systolic and diastolic blood pressures, and the presence or absence of albumin and casts in the urine. Practically all blood pressure observations were made by the same individual, and the beginning of the fourth phase was accepted as the diastolic pressure.

DISCUSSION

The average daily excretion of dimethyl-guanidine in the thirteen cases of hypertension was 105 mgm. This was lower than that found in the normal subjects, namely 119 mgm., but equal to that found by Major in normal subjects. Since with our present knowledge the variables affecting excretion of guanidine bases are not known one cannot accurately determine which deviations from the "means" are purely fortuitous. Application of statistical methods to the phenomenon of variation observed here would therefore yield information of limited significance. It is merely stated that a glance at both tables 1 and 2, shows that in the majority of instances the low average values of guanidine excretion are associated with the high values of the diastolic blood pressures. This is of interest in view of the suggested mechanism by means of which the guanidine compounds raise the blood pressure, namely, by peripheral constriction of the arterioles.

Daily observations were made in one case over a period of two weeks. The subject, a female, aged 35 years, was admitted into the Medical Service of one of the writers (C. P. H.) on October 6, 1925. The clinical picture was that of chronic interstitial nephritis, associated with syphilis. There was marked thickening of the blood vessels, cardiac hypertrophy, and some retinal changes. Blood pressure: systolic 250, diastolic 160. The urine contained albumin and casts. The blood urea nitrogen was 14 mgm. per 100 cc. blood, creatinine 1.20 mgm. per 100 cc. The urea concentration factor was 16.

The patient was kept in bed throughout the period of observation and on a constant diet. Daily examinations were made with reference

to blood pressure and the excretion of water and guanidine. When the blood pressure tended to remain at a constant level following the initial fall due to rest in bed, calcium chloride was given in doses of 5 grams three times a day. The above daily examinations were continued. The results are recorded in table 3. It will be noted that during the first four days, though the systolic blood pressure fell from 250 to 220 mm. and the diastolic pressure fell from 160 to 125 mm. there was no increase in the excretion of guanidine. This was con-

TABLE 3

Blood pressure, excretion of urine and dimethyl-guanidine in a case of chronic interstitial nephritis. (Case 4742-25)

Date	Blood pressure		Dally excretion of dimethyl-guanidine	Volume of urine
	Systolic	Diastolic		
			mgm.	*cc.*
October 6	250	160	74	950
October 7	205	130	45	1,400
October 8	220	130	82	870
October 9	220	125	68	920
October 10*	225	130	112	2,400
October 11	210	135	386	3,550
October 12	185	125	240	2,620
October 13	180	120	318	3,000
October 14			194	2,990
October 15			206	3,900
October 16	178	122	370	2,800
October 17	180	118	385	2,800
October 18	170	115	294	3,100
October 19	180	110	192	1,600

* Calcium chloride treatment (5 grams t.i.d.) commenced.

trary to that expected if there is perfect correlation between guanidine excretion and blood pressure. During this period *there was no polyuria.* Following the institution of the calcium chloride treatment (October 10) both the systolic and diastolic pressure fell still further. *This was accompanied by a marked diuresis,* and the excretion of guanidine bases was increased. Urine volume output therefore appeared to influence excretion in this case. The fact is merely mentioned that following calcium chloride treatment a lowering of the blood pressure occurred. It does not necessarily follow that this was caused by the

treatment. As a matter of fact we have sufficient data proving the inefficacy of this therapeutic measure.

In view of all the above findings, the relationship between arterial hypertension and decreased guanidine excretion is suggestive, and on the whole, there is some corroboration of the work of Major and his associates, on the relation between increased guanidine excretion and diuresis. However, the fact that some individuals with marked hypertension excrete normal amounts of guanidine bases, and that in the case reported above (No. 4742) the fall in blood pressure during the earlier period of observation was not accompanied by an alteration in the excretion of these substances, warns us that more must be known of this relationship.

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