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PROBABLE ERRORS IN THE SIMULTANEOUS MEASUREMENT OF SEPARATE KIDNEY FUNCTIONS

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The methods developed by Smith and his associates have made possible the separate measurement of glomerular filtration, the effective renal blood flow, and the total functioning mass of tubular tissue (1). During a recent study of the effects of certain steroids on these renal functions in man, it became apparent that their determination could not always be made simultaneously since the administration of test substances for the determination of one function interfered with the determination of another. The extent and manner of this interference is the subject of the present communication.

METHODS

A. The plasma clearance of mannitol (C_M) was used as a measure of glomerular filtration (1). Plasma levels of the compound were maintained between 90 and 200 mgm. per cent.

B. The plasma clearance of p-amino hippuric acid (PAH) at levels of from 0.8 to 3.0 mgm. per 100 ml. plasma was used as an index of effective renal blood flow. At these levels, PAH is removed completely from the plasma in a single passage through the kidney (2).

C. The functioning tubular mass (Tm) was ascertained by two methods. These were: (1) p-Amino hippuric acid Tm (Tm_{PAH}), a measure of the maximum ability of the kidney tubules to secrete that substance (3); plasma levels greater than 44 mgm. per cent were maintained during the determination. (2) Glucose Tm (Tm_G), a measure of the maximum ability of the tubular cells to reabsorb glucose (4, 5) in the course of these determinations; plasma levels of glucose were maintained constantly above 300 mgm. per cent.

Solutions of the test substances were made before each determination from amounts calculated to be necessary to raise and maintain the desired concentration in the plasma (5). After preliminary trial procedures, these amounts were adjusted. Those solutions used for "priming" were run in by gravity through a No. 18 gauge needle as rapidly as possible. Those solutions used to maintain the desired plasma levels were given at about 4 ml. per minute and, after 15 minutes, blood and urine collections were begun.

Each function was estimated during 3 consecutive 10-minute periods. Blood samples were taken at the onset and just prior to the completion of the last of these periods.

Urine was collected through an indwelling catheter and, after each collection, the bladder was washed out 2 times with 20 ml. of saline and 10 ml. of air. All chemical determinations were made within 36 hours of the clinical tests. Protein-free filtrates of plasma samples were made as soon as each test was completed.

CLINICAL MATERIAL

A heterogeneous group of 13 subjects was studied. These consisted of 3 normal women, 2 normal men, 1 woman with chronic hypertension, and another with carcinoma of the uterus, 1 male with Paget's disease of the bone, 1 with melanosarcoma, 1 with hypogonadism, and 1 each with cancer of the stomach, breast, and prostate. All subjects were afebrile and in good nutritional status.

RESULTS

A. *The relationship of the plasma concentration of glucose to the clearance of p-amino hippuric acid and mannitol*

Measurements of PAH clearance were first made in 4 subjects. When several days later these determinations were repeated, the values in 3 apparently had decreased by amounts varying from 16 to 63 per cent. This unusual finding was considered possibly due to the fact that an attempt was made during the latter determination to measure simultaneously the glucose Tm and for that purpose, it was necessary to maintain plasma levels of glucose at from 390 to 500 mgm. per cent (Table I).

It became necessary, therefore, to ascertain whether or not the renal clearance of PAH could have been affected merely by this increased concentration of glucose in the plasma, or due to some other factor which had developed between the first and second measurements. Accordingly, the C_{PAH} was determined in the course of a single test in 3 subjects, both before and during the infusion of glucose. In 1 of these, the test was repeated. A decreased clearance of PAH was effected in 3 experiments within a few minutes after the plasma glucose

level was raised to levels of from 390 to 520 mgm. per cent. This depression was constant in several consecutive 15-minute periods (Table I) and ranged from 30 to 80 per cent.

The possibility existed that the apparent depression of renal blood flow which had occurred when the plasma glucose level was increased might have been due to an interference in the determination of PAH by the presence of large concentrations of the sugar. However, known concentrations of PAH (0.5 to 5.0 mgm. per cent) in the presence of larger concentrations of glucose always could be quantitatively and completely recovered.

It is of interest to note that the clearance of mannitol, on the other hand, was not significantly affected by wide alterations in the plasma glucose level (Table I).

B. The relationship between the plasma concentrations of p-amino hippuric acid to the tubular resorption of glucose (Tm_G)

Measurements of the tubular resorption of glucose were made in 5 individuals, at which time their plasma levels of p-amino hippuric acid ranged from 0.5 to 1.8 mgm. per cent. In 2 instances, an attempt was made on another day

to measure simultaneously the Tm of glucose and of PAH. In the remaining 3, and also in 1 of the preceding 2 individuals, the measurement of Tm_{PAH} was made simultaneously with that of glucose, immediately after the glucose Tm had been determined alone. During this determination, the concentrations of PAH in the plasma necessarily were increased to levels of from 44 to 81 mgm. per cent. Under these circumstances, the value of glucose Tm apparently was increased significantly in 3 individuals by from 22 to 68 per cent (Table II). In these 3 subjects, the increased Tm values persisted until the plasma concentration of PAH again was sharply reduced.

The addition of PAH in concentrations of from 1 to 100 mgm. per cent to solutions of glucose was not found to interfere with the quantitative determinations of the sugar.

C. The relationship of the plasma level of glucose to the apparent tubular secretion of PAH

In 8 subjects, an attempt was made to ascertain the effects of high concentrations of glucose on the apparent tubular secretion of PAH. These measurements were obtained on the same day in all but 2 instances. In the course of the

TABLE I
The effect of the plasma concentration of glucose on the clearance of p-amino hippuric acid and mannitol

Subject	Tests made on	Plasma concentration			Plasma clearance	
		Glucose	PAH	Mannitol	PAH	Mannitol
		<i>mgm. per cent</i>			<i>ml. per minute</i>	
M. H. Hypogonadism	Separate days	Fasting	2.3	180	387	81
		495	1.7	176	162	78
M. F. Hypertension	Separate days	Fasting	2.9	200	215	73
		500	1.6	166	180	75
E. C. Normal	Separate days	Fasting	1.4	175	635	107
		390	1.6	150	235	120
A. B. Melanosarcoma	Separate days	Fasting	1.6	147	543	129
		455	1.2	140	681	119
F. S. Cancer stomach	Same day	Fasting	0.61	99	630	112
		520	0.52	115	433	122
E. C. Normal	Same day	Fasting	1.5	135	750	100
		450	1.8	130	170	126
	Same day	Fasting	1.2	123	830	115
		390	1.3	128	372	121
G. F. Cancer, prostate	Same day	Fasting	1.35	123	728	122
		346	1.2	135	932	132

TABLE II
The effect of the plasma concentration of PAH on the tubular reabsorption of glucose

Subject	Tests made on	Plasma level			Tm	
		PAH	Mannitol	Glucose	Glucose	PAH
M. H. Hypogonadism	Separate days	70.0	205	550	185	52
		1.65	190	520	152	
E. C. Normal	Separate days	66.5	185	495	215	70
		1.30	145	350	175	
	Same day	1.8	130	450	172	55
		81.0	155	380	290	
F. S. Cancer, stomach	Same day	0.5	115	520	321	72
		44.0	136	570	440	
A. B. Melanosarcoma	Same day	1.2	140	455	297	78.9
		68.0	140	433	314	
G. F. Cancer, prostate	Same day	1.2	135	346	340	81.3
		55.0	137	375	351	

determinations, the plasma levels of PAH were maintained at concentrations of from 54 to 176 mgm. per cent.

When the plasma glucose level was raised from the fasting levels to that necessary to ascertain the Tm value (from 375 to 533 mgm. per cent), a decrease in the Tm_{PAH} was effected in 3 individuals. This decrease ranged from 17 to 48

per cent. No change occurred in 1 subject, and in the remaining 4, the decrease probably was not significant (Table III).

D. The relationship between the plasma levels of glucose and PAH and the clearance of mannitol

In the course of the determinations described, whenever the plasma concentrations of both

TABLE III
The effect of the plasma concentration of glucose on the tubular secretion of PAH

Subject	Tests made on	Plasma level			Tm	
		Glucose	PAH	Mannitol	PAH	Glucose
		mgm. per cent			mgm. per minute	
C. W. Normal	Same day	Fasting 394	81 81	130 142	78.0 74.1	184
E. S. Cancer, breast	Same day	Fasting 533	170 176	218 223	34.6 17.9	190.9
E. C. Normal	Same day	Fasting 413	86.5 66.5	150 148	81.8 74.2	234.3
F. G. Normal	Same day	Fasting 520	73.0 54.0	160 163	89.6 74.3	360
R. M. Normal	Same day	Fasting 525	80.0 63.0	150 150	80.0 76.5	310
D. F. Paget's disease	Same day	Fasting 492	72.0 68.0	150 160	96.4 76.8	260
G. F. Cancer, prostate	Separate days	Fasting 375	59.0 55.0	130 137	90.4 81.3	351
A. B. Melanosarcoma	Separate days	Fasting 433	67.5 68.0	140 140	78.2 78.9	314

TABLE IV

The effect of the plasma concentration of glucose and PAH on the glomerular filtration of mannitol

Subject	Tests made on	Plasma concentration			Mannitol clearance
		Glucose	PAH	Mannitol	
E. C. Normal	Separate days	Fasting	2.0	140	100
		380	81.0	155	145
	Same day	Fasting	1.9	143	102
		413	66.5	148	122
F. S. Cancer, stomach	Same day	Fasting	1.8	100	112
		560	44.0	140	145
D. F. Paget's disease	Separate days	Fasting	2.1	143	86.5
		492	68.0	163	96.0
G. W. Normal	Same day	Fasting	1.6	135	90
		394	81.0	142	107
E. S. Cancer, breast	Same day	Fasting	2.8	200	49
		533	165.0	223	72
F. G. Normal	Same day	Fasting	1.7	157	102
		520	54.0	163	120

glucose and PAH were simultaneously increased, there occurred in all of 6 subjects studied, a significant increase of the mannitol clearance. This increase ranged from 11 to 47 per cent (Table IV). That this finding was not due to any interference with the chemical determinations of mannitol was demonstrated by the quantitative recoveries of that compound from solutions containing high concentrations of both glucose and PAH.

COMMENT

The rate of glomerular filtration (C_M), effective renal blood flow (C_{PAH}), and apparent tubular excretory or absorption mass (Tm_{PAH} and Tm_G) probably are constant for a given individual who remains untreated or does not suffer from a progressive renal or vascular disease (5). For this reason, their measurement has been advocated to evaluate expected changes of separate components of kidney function. It would appear, however, from the present study that the value of certain functions sometimes may be altered by an attempt to measure simultaneously a second renal capacity. Hence, unless successive observations on the same subject are repeated under identical conditions, the determinations frequently may be in error.

It is impossible to explain definitely the alterations of Tm and clearance values when the plasma concentrations of glucose or PAH reach high levels. With regard to the mannitol clearance, which is uncomplicated by tubular transfer phenomena, one must look to changes in the glomerular apparatus for the explanation of increased C_M values when plasma concentrations of both glucose and PAH are raised. Specifically, one must consider changes in renal blood flow and distribution due to alterations in tone of the afferent and efferent arterioles, changes in systemic blood pressure and the possibility of variations in the number of functioning nephrons under the various conditions.

The alterations in those functional activities which depend in part or wholly on the active transfer mechanisms in the cells of the proximal segments of the tubules are more difficult to interpret. Recently there has been demonstrated (6) a nonspecific interference of sodium chloride and potassium chloride with the tubular reabsorption of ascorbic acid. These findings and those of the present study seem to indicate a competition of chemically unrelated substances for the cellular transfer mechanisms. The actual characteristics of this competition are not clear but their functional significance is potentially very great.

CONCLUSIONS

1. High plasma concentrations of glucose may decrease the apparent renal blood flow as determined by the clearance of p-amino hippuric acid.
2. High plasma concentrations of glucose do not alter the rate of glomerular filtration (C_M) but may decrease the maximum ability of the tubules to secrete p-amino hippuric acid.
3. High plasma concentrations of p-amino hippuric acid may increase the apparent tubular resorption of glucose.
4. When the plasma concentrations of both glucose and p-amino hippuric acid are raised, increased values of apparent glomerular filtration are obtained.
5. The simultaneous measurement of more than one renal function frequently may give erroneous values.

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