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Research Article

THE ACTION OF PHLORIZIN ON THE EXCRETION OF GLUCOSE, XYLOSE, SUCROSE, CREATININE AND UREA BY MAN

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Although phlorizin has been used mostly in the lower animals, its administration to man is not without precedent; shortly after its isolation by de Koninck (1836a, b), this investigator tried it in the treatment of malaria on the ground that it was bitter, like other remedies which were effective in this disease. The use of the drug in this connection was short-lived, however, and it was not until many years later that v. Mering (1885) discovered that it caused glycuresis and diuresis, observations which initiated its application in the treatment of nephritis, sarcoma, etc., and as a test for renal function in man, in addition to its well known use in studies of metabolism. Since these instances of human administration are of some interest, we have summarized them in Table I.

The largest dose *per os* appears to be 15 grams in wafer-form, reported by Pietkiewicz (1869) and v. Mering (1889), while Korte (1896) took three five-gram doses dissolved in alcohol in one day. v. Mering (1889) also records the largest parenteral dose (in a case of sarcoma): 2 grams (in warm aqueous solution) injected subcutaneously daily, one gram in the morning and one gram in the evening, for a period of thirty days. Benedict and Lewis (1913—personal communication) gave 2 grams daily in 10 cc. of sterile olive oil subcutaneously over a period of days. In no instance was permanent injury described.

Moderate intravenous doses of the drug produce no unfavorable reactions in the dog, and we decided that the intravenous route would be the most satisfactory for our purposes, particularly since we wished to determine the exact effect of small doses. Our anticipation in this matter has been justified, since we have given phlorizin in doses varying from 2.0 to 65.0 mgm. per kgm. with no unfavorable reactions other than an apparent diminution in glomerular activity with the larger doses. We feel called upon, however, to express a word of caution about the use of the intravenous technique in man and refer the reader to the description of our method of preparation and administration. Previous observations from this laboratory have shown that in the dog adequate doses of phlorizin raise the glucose clearance and lower the creatinine clearance to the level of the xylose clearance (Jolliffe, Shannon and Smith

TABLE I

Administration of phlorizin to man

Investigator	Date	Mgm. per man per diem	Route of administration
de Koninck	1836	1,600	Per os; divided doses
v. Coetsem	1836	1,600	Per os; one dose
Mareska	1836	1,600	Per os; 2 doses
de Muynck	1836	1,250	Per os; ?
Hanegraeff	1836	1,600	Per os; one dose
Pietkiewicz	1869	15,000	Per os; one dose
v. Mering	1889	15,000	Per os; one dose
Klemperer	1896	10,000	Per os; one dose
Korte	1896	15,000	Per os; 3 doses
v. Mering	1889	2,000	Hypodermic; 2 doses, for 30 days
Magnus-Levy	1896	1,000	Hypodermic; ?
Achard and Delamare	1899	50	Hypodermic; one dose
Delamare	1899	50	Hypodermic; one dose
Casper and Richter	1900	?	Hypodermic; one dose
Allard	1907	200	Hypodermic; one dose
Tanaka	1908	10	Hypodermic; one dose
Benedict and Lewis	1913	2,000	Hypodermic; one dose, repeatedly*
Chabanier and Lobo-Onell	1913	25	Hypodermic; one dose
Grote	1921	10	Hypodermic; one dose
Kamnitzer and Joseph	1921	2.5	Hypodermic; one dose
Hetényi	1922	60	Hypodermic; one dose
Rosenberg	1923	50	Intramuscular; one dose
Kamnitzer and Joseph	1924	2	Intramuscular; one dose
Dünner and Mecklenburg	1925	4.4	Hypodermic; one dose
Dünner and Kronenberger	1930	10	Intramuscular; one dose
Present experiments	1933	3,800	Intravenous; one dose

* In oil (personal communication).

(1932) and Shannon, Jolliffe and Smith (1932)). Our present experiments were designed to determine if similar changes in the glucose and creatinine clearances occur in man. Large doses of the drug were avoided, and different individuals were employed for each test.

METHODS

Our subjects were convalescent patients, with normal renal function, kept in bed throughout the morning of the experiment. The routine of the experiments listed in Table II was as follows:

The patient was allowed no breakfast. At zero minutes 70 grams of xylose were given in 10 tablespoons of oatmeal (no milk or sugar) and shortly afterward 10 grams of creatinine were taken in water. (N.B. The administration of xylose in oatmeal circumvents the diarrhea which frequently follows its administration in aqueous solution and generally gives a flat blood sugar curve.) Varying amounts of water were given at zero, 30 and 60 minutes, and at 90 minutes the bladder was emptied (*vide infra*) and the first urine collection period begun. After one or more control periods phlorizin was injected

intravenously. During the next few minutes (washout period) normal saline was instilled into the bladder and removed with the discard. Three more specimens of urine were then collected at intervals of 20 to 30 minutes each.

In the experiments listed in Table III the above routine was modified to permit the intravenous injection of sucrose. At zero minutes 500 cc. of water were taken, followed by 70 grams of xylose in 10 tablespoons of oatmeal; at 50 minutes an intravenous infusion of 10 per cent sterile sucrose solution (in distilled water) was begun, 600 cc. being injected over a period of 30 to 50 minutes. Immediately after this injection, phlorizin was administered intravenously.

Urine was collected by catheterization in dry flasks containing a little benzoic acid, with special care to secure complete emptying of the bladder. Samples of blood were taken from the antecubital vein as near to the middle of each urine collection period as possible. The blood was centrifuged and the plasma precipitated at once. All plasma concentrations were interpolated to the exact middle of the urine collection period and no correction was made for urinary dead-space.

Phlorizin, repurified by the method of Deuel and Chambers (1925), was weighed out in advance of the experiment. Just before use the phlorizin was dissolved in hot, freshly boiled 2.5 per cent $NaHCO_3$, and while still warm the solution was injected into the antecubital vein. In those experiments where the dose of phlorizin was greater than 2.5 grams, it was necessary to weigh the drug in two portions and to dissolve them separately. (Otherwise the solution cools and the drug recrystallizes during the injection.)

The chemical methods used were those of Jolliffe, Shannon and Smith (1932) and Shannon, Jolliffe and Smith (1932). Sugar and creatinine analyses were done twice in all experiments except those on T.S., M.W., and M.M.; the deviation between the two analyses was slight, and the recorded figures are in every case averages of the two determinations.

Our experiments are divisible into two groups, in the first of which (Table II) the effects of single doses of phlorizin on the urea, glucose, xylose, and creatinine clearances were followed. Two control samples of blood and urine were collected prior to the injection of phlorizin; after a washout period of 20 to 50 minutes to clear the dead-space of the kidneys, ureters and bladder, three more samples of urine and additional samples of blood were collected to enable us to observe the effects of phlorizin over a period of 40 to 60 minutes.

The second group of experiments was designed to examine the effects of increasing doses of phlorizin on the glucose, xylose and sucrose clearances (Table III). The arrangement of these experiments was similar to those of the first group except for the omission of control periods.

In the first group of experiments 11.8 mgm. of phlorizin per kgm. raised the glucose clearance for at least one hour to the level of the xylose clearance, and 65.2 mgm. per kgm. did not raise the former significantly above the latter. In accordance with the observations previously published from this laboratory, we interpret these results to indicate that the last four individuals in Table II were "completely phlorizinized," i.e., the tubular reabsorption of glucose was completely blocked.

TABLE II

Simultaneous xylose, glucose, urea and creatinine clearances in man following intravenous administration of phlorizin

Subject	Phlorizin	Surface area	Total concurrent time	Urine flow per minute	$\frac{UV}{P}$/S.A.				Creatinine / Xylose	Urea / Xylose	Glucose / Xylose
					Xylose	Glucose	Creatinine	Urea			
	mgm. per kilo	*sq. m.*	*minutes*	*cc.*							
T.S. ♂	2.04	1.51	35	1.30	20.4		35.9	14.6	1.76	.72	
			54	.95	17.9		31.0	11.6	1.73	.65	
			79	.88	14.1		26.0	9.8	1.84	.69	
			105	Washout period							
			141	2.17	22.6	13.0	33.2	15.0	1.47	.66	.58
			183	1.10	15.9	4.2	23.0	9.6	1.45	.60	.26
M.W. ♀	4.12	1.18	21	1.00	53.0		104.3	38.4	1.97	.72	
			37	1.50	64.7		128.5	49.1	1.99	.76	
			80	Washout period							
			99	4.60	55.0	35.2	106.0	46.1	1.96	.84	.64
			117	5.55	59.0	36.6	113.5	48.2	1.92	.82	.62
			138	5.76	59.1	30.8	122.4	47.1	2.07	.80	.52
M.M. ♀	6.07	1.52	31	3.20	18.4		43.2	14.5	2.35	.79	
			63	3.20	34.3		78.5	26.5	2.29	.77	
			90	Washout period							
			121	2.60	30.8	31.0	65.1	26.8	2.11	.87	1.01
			150	3.60	37.6	34.6	86.4	32.5	2.30	.86	.92
			179	3.10	36.5	15.3	83.2	30.2	2.28	.83	.42
A.H. ♀	11.8	1.27	18	12.70	58.0		106.7	44.0	1.84	.76	
			74	Washout period							
			94	3.20	49.1	50.3	86.2	38.8	1.76	.79	1.02
			114	3.10	52.2	55.2	93.6	40.3	1.79	.77	1.06
			139	2.90	55.4	57.6	94.0	40.8	1.70	.74	1.04
M.S. ♀	15.7	1.39	25	1.60	53.5		96.3	41.7	1.80	.78	
			72	Washout period							
			90	1.67	43.9	45.4	75.5	31.0	1.72	.71	1.03
			104	1.63	42.3	44.2	73.0	30.7	1.73	.73	1.04
			130	1.75	48.6	48.3	81.2	34.3	1.67	.71	.99
C.S. ♀	20.4	1.47	21	7.30	58.6		109.5	34.3	1.87	.58	
			41	2.60	60.8		112.3	35.4	1.85	.58	
			74	Washout period							
			94	2.37	52.4	54.0	105.5	30.6	2.01	.58	1.03
			115	2.25	55.4	56.0	108.5	33.1	1.96	.60	1.01
			139	2.26	58.0	56.8	110.9	34.9	1.91	.60	.98
N.O. ♀	65.2	1.60	20	9.70	43.0		76.3	33.1	1.77	.77	
			44	6.62	41.4		82.5	34.3	1.99	.83	
			91	Washout period							
			106	2.08	30.8	33.4	46.3	20.0	1.50	.65	1.08
			126	2.10	32.9	34.3	49.9	20.7	1.52	.63	1.04
			145	1.94	30.2	32.6	48.6	19.4	1.61	.64	1.08

TABLE III

Simultaneous xylose, sucrose and glucose clearances in man following intravenous administration of phlorizin

Subject	Phlorizin	Surface area	Total concurrent time	Urine flow per minute	$\frac{UV}{P}$/S.A.			Glucose / Xylose	Sucrose / Xylose
					Xylose	Glucose	Sucrose		
	mgm. per kgm.	*sq. m.*	*minutes*	*cc.*					
A.V. ♀	21.7	1.58	18	6.64	57.1	45.8	56.0	0.80	0.98
			39	5.38	58.6	48.0	54.4	0.82	0.93
			60	4.41	50.6	43.2	48.5	0.85	0.96
			80	4.20	49.3	36.1	47.4	0.73	0.96
F.M. ♀	29.7	1.32	19	4.30	55.7	50.9	53.8	0.91	0.97
			39	3.95	55.4	55.4	53.6	1.00	.97
			64	3.48	53.3	54.1	54.3	1.02	1.02
V.T. ♀	41.9	1.59	31	4.90	46.8	41.0	45.0	0.88	0.96
			51	3.80	37.8	34.7	35.6	.92	.94
			75	5.79	48.4	45.5	48.4	.94	1.00
W.M. ♂	45.3	1.49	20	4.02	42.0	39.8	42.0	0.95	1.00
			43	3.97	47.0	45.9	46.1	0.98	.98
			66	4.09	49.5	48.1	50.0	0.97	1.01
			87	3.77	47.8	48.1	47.4	1.01	.99
F.M. ♀	59.4	1.32	29	4.30	55.1	56.0	58.6	1.02	1.06
			54	3.56	57.2	57.7	61.4	1.01	1.07
			82	2.86	46.2	44.8	48.5	.97	1.05
			104	2.18	44.3	44.0	45.7	.99	1.03

In the experiments listed in Table III, in which the comparison of xylose and sucrose was made, 21.7 mgm. per kgm. were apparently inadequate to produce complete glycuresis, but the variations in the glucose : xylose ratio after larger doses must be considered to be within the experimental error. Again we pushed on to large doses to see if any one of the three sugars might be preferentially affected, but we find no evidence that such is the case. If xylose or sucrose were reabsorbed by the renal tubules, it might be imagined that a small dose of phlorizin would bring the glucose clearance up to the xylose clearance, while larger doses would raise the former definitely above the latter. To the contrary, it would seem that once the reabsorption of glucose is completely blocked, the simultaneous glucose, xylose and sucrose clearances remain identical within the experimental error, regardless of the quantity of phlorizin administered. In view of this fact, and in view of the further facts that the xylose clearance is not raised significantly in respect to the urea clearance, nor in respect to its own control level,[1] by the

[1] The single exception to this statement occurred in T.S., who received the smallest dose of phlorizin given.

administration of phlorizin, we conclude that in man, as in the dog, the xylose (or sucrose) clearance is a measure of glomerular filtration (*cf.* Jolliffe, Shannon and Smith, 1932).

Since, by the above interpretation, "complete phlorization" consists of a change in renal activity whereby all the glucose filtered at the glomeruli is allowed to pass into the urine, and since the term "complete phlorization" is open to several objections, we prefer to designate this condition as "complete glycuresis," in line with the use of this term as suggested by Benedict, Osterberg and Neuwirth (1918) to designate the increased rate of excretion of glucose, rather than the mere presence of this substance, in the urine. Thus, we are able to speak of complete glycuresis, transient glycuresis and recovery from glycuresis, a more flexible usage than is possible with the older term.

The fact that the urea clearance is consistently lower than the xylose clearance is uninterpretable at the present time. The urea : xylose ratios observed throughout this work confirm in general the observation of Jolliffe and Chasis (1933) and Keith, Power and Peterson (urea : sucrose, 1933) on man, and our own observations on the dog.

With regard to the effect of phlorizin on the creatinine clearance in man it will be noted that the administration of the drug resulted in a drop in the creatinine : xylose ratio only in subjects T.S. and N.O. Since equally large variations in this ratio have been observed during the course of single experiments in man (unpublished details of Jolliffe and Chasis, 1933), we cannot attach particular significance to this result, and we conclude that larger doses of phlorizin are required to reduce the creatinine clearance to the level of the xylose clearance (i.e. to depress completely the tubular secretion of creatinine) than are required to produce complete glycuresis. It would be of interest to know if complete depression of creatinine secretion could be obtained in man as in the dog, but we decided that the question did not justify the administration of intravenous doses larger than those we have given.

In conclusion, it may be noted that the glycuresis induced in man by phlorizin is transient, as is the case in the dog. All our subjects were tested for glycosuria at intervals following the formal observations, and found to be essentially sugar-free within 24 hours.

SUMMARY

The minimum intravenous dose of phlorizin required in man to produce complete phlorization (i.e., to raise the glucose clearance to xylose clearance) was found to be in the neighborhood of 10 to 20 mgm. per kgm.

Sixty-five mgm. per kgm. did not raise the glucose clearance above the xylose clearance, and 59.4 mgm. per kgm. did not cause deviation between the xylose and sucrose clearances. Neither did the phlorizin

cause a significant rise in the xylose clearance as compared to control periods taken just before the administration of the drug.

In the largest dose which we have given (65.0 mgm. per kgm.) the drug exerted no significant depressive action on the ratio of creatinine : xylose clearance.

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