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THE EFFECTS ON RENAL ACTIVITY OF THE ORAL ADMINISTRATION OF PHLORIZIN IN MAN

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Chasis, Jolliffe and Smith (1) have shown that phlorizin administered intravenously to man, raises the level of the glucose clearance to that of the simultaneous xylose and sucrose clearances, the duration of this effect depending upon the size of the dose. In the largest doses given, the creatinine clearance was not significantly affected with respect to the clearances of the non-metabolized sugars.

It appeared desirable to investigate the effects of phlorizin when administered by mouth. It seemed possible that, if the phlorizin were well absorbed, complete glycuressis might be maintained for considerable periods of time by the repeated administration of small doses and that under these conditions the clearances of creatinine, glucose and xylose might be brought together, as happens in the dog after larger doses of phlorizin (2). Chasis, Jolliffe and Smith (1) have reviewed the literature on the oral administration of phlorizin in man, but in none of this previous work have the recorded observations made it possible to evaluate the effects upon the glucose clearance.

Volunteers for this study were obtained from the Third (New York University) Medical Division of Bellevue Hospital. During the period of observation they were segregated and under the care of a special nurse. The subjects were maintained on the regular ward diet and the phlorizin tests were performed before breakfast, with the subject recumbent in bed. Blood was drawn from the antecubital vein, heparin being used as an anti-coagulant. The blood was centrifuged and the plasma precipitated immediately. All urine discards and observation specimens were removed by catheter and collected in flasks containing a few benzoic acid crystals. Appropriate dilutions were made subsequently, and plasma and urine were analyzed by the methods of Jolliffe, Shannon and Smith (3).

The usual procedure was as follows: 100 grams of xylose and 10 grams of creatinine were mixed with about 10 tablespoons of oatmeal or dissolved in 200 cc. of water. This was taken by the subject at 7:30 a.m.; at 9 a.m. the bladder was catheterized for the first discard and immediately there-

TABLE I
Simultaneous xylose, glucose, urea and creatinine clearances in man before and after oral administration of phlorizin

Subjects	Surface area <i>square meters</i>	Phlorizin <i>mgm. per kilo</i>	Time from phlorizin <i>minutes</i>	Number of periods averaged	Average urine volume <i>cc. per minute</i>	Average clearance				Clearance ratios			
						Xylose	Urea	Creatinine	Glucose	Urea Xylose	Creatinine Xylose	Glucose Xylose	
M. O'L.	1.7	150	Control 18-95	2	7.60	<i>cc. per sq. m. per minute</i>	Xylose	Urea	Creatinine	Glucose	Urea Xylose	Creatinine Xylose	Glucose Xylose
							48.7	34.3	106.0		0.70	2.18	
							40.7	25.3	77.6	30.8	0.62	1.90	0.76
							52.4	38.4	101.8		0.73	1.94	
M. C.	2.08	200	Control 160-250	4	1.57	<i>cc. per sq. m. per minute</i>	Xylose	Urea	Creatinine	Glucose	Urea Xylose	Creatinine Xylose	Glucose Xylose
							36.5	23.3	66.8	18.4	0.64	1.83	0.50
							55.3	31.1	90.4		0.56	1.63	
							33.3	14.4	47.3	32.6	0.43	1.42	0.98
		400	Control 240-350	2	2.54	<i>cc. per sq. m. per minute</i>	Xylose	Urea	Creatinine	Glucose	Urea Xylose	Creatinine Xylose	Glucose Xylose
							52.2	31.8	96.5	21.7	0.61	1.85	0.54
		400		4	1.73	<i>cc. per sq. m. per minute</i>	Xylose	Urea	Creatinine	Glucose	Urea Xylose	Creatinine Xylose	Glucose Xylose
							40.2	20.1	61.6	0.50	1.53	0.54	

after the first blood sample was drawn. At 9:15 the first urine sample was collected. At 9:30 a.m. the second urine sample and the second blood were obtained. Two control periods being completed, repurified phlorizin was administered as a suspension in water, or where feasible, as a solution in whiskey. At 10 a.m. the bladder was catheterized for the second discard (washout) and the third blood sample was drawn. At 10:15 a.m. and 10:30 a.m. respectively the third and fourth urine samples were removed by catheter. At 10:35 a.m. the fourth blood sample was drawn. At 10:45 a.m. the fifth urine sample was obtained. At 11 a.m. the sixth urine sample and the fifth blood were obtained, completing the experiment. From the first two values for urea, creatinine, glucose and xylose in blood an interpolation was made to the midpoints of the two control periods and from the last three values interpolations to the midpoints of the four test periods.

It was found in two preliminary series of observations in which 50 mgm. and 100 mgm. of phlorizin per kgm. (dissolved in whiskey) were administered, that the resulting glycuressis reached a maximum within 30 minutes and disappeared within 6 to 7 hours. It was apparent that anything approaching complete glycuressis could only be obtained by the repeated administration of fairly large doses. A summary of glucose, xylose and creatinine clearances observed simultaneously is given in Table I. In the first instance the phlorizin was given in a single dose; in the others in four divided doses at approximately 45 minute intervals. The quantity of phlorizin administered in the last two instances (four doses of approximately 8 grams each) is all that can be taken conveniently by stomach because of the large volume of fluid required. It is clear that this quantity of phlorizin is inadequate to raise the glucose clearance to the level of the xylose clearance with any certainty, and it is concluded that although partial glycuressis can be obtained readily for short periods of time by small doses of phlorizin administered orally, it is practically impossible to obtain complete glycuressis by this procedure.

Our data show that the clearances of urea, creatinine and xylose are all depressed after large doses of phlorizin, indicating a reduction in glomerular activity such as was observed after the intravenous administration of this drug in man by Chasis, Jolliffe and Smith (1), in the dog by Shannon, Jolliffe and Smith (2) and in the sculpin (in which the glomeruli may be completely closed by large doses of phlorizin) by Marshall and Grafflin (4). It would appear that this effect upon glomerular activity is a characteristic though rather variable feature in the physiological action of this drug. This depressant effect upon glomerular activity, and transient nausea with the larger doses, were the only unfavorable symptoms noted in these observations. In all instances the urine was free from sugar and otherwise normal for several days afterward. Our results do not warrant the belief that the administration of phlorizin by mouth over mod-

erate periods of time significantly affects the creatinine clearance relative to the xylose clearance.

SUMMARY AND CONCLUSION

The oral administration of phlorizin in man produces a transient glycosuria, but the largest practical doses (approximately 400 mgm. per kgm. divided into four doses at 45 minute intervals) are inadequate to raise the glucose clearance to the level of the xylose clearance with any certainty, nor do they lower the creatinine clearance to the level of the glucose or xylose clearances.

Oral administration of the drug is apparently much less efficient than intravenous injection in producing complete glycosuria.

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