THE RENAL EXCRETION OF DIGOXIN IN THE NORMAL YOUNG SUBJECT [1]

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Following the introduction of the embryonic duck heart assay method (1), and the radioactive isotope tracer technique (2), means were available for the quantitative study of the renal excretion of various cardioactive glycosides in both the experimental animal and man. It was but natural that the renal excretion of the digitalis glycoside, digitoxin, received the first attention of both the investigators employing the embryonic heart assay and those utilizing the radioactive method. Both groups agree exactly (3, 4) upon the amount of digitoxin excreted by man during the first 24 hours after administration. They also agree that the major portion of a given dose is destroyed and not excreted as intact digitoxin or a cardioactive metabolite of it. There is, however, some discrepancy in the quantitative estimates obtained by each group concerning the amount of cardioactive glycoside excreted after the first day of administration. This latter disagreement could be due to the fact that the group utilizing the embryonic duck heart method studied the renal excretion of glycoside in *young,* normal subjects, whereas the other group studied the same function in aged patients suffering from cardiac failure, subjects who have been found (3) to excrete far less unchanged digitoxin than the normal young subject.

Thus, if some information has been obtained about the renal excretion of digitoxin, no quantitative studies have been done concerning the renal excretion of other useful, frequently employed cardioactive glycosides. One of these is digoxin, whose excretion has been assumed to be far more rapid than that of digitoxin. This belief is based upon the comparative rapidity with which both the therapeutic and toxic effects of digitalization disappear after cessation of administration of the drug (5). However, no quantitative renal measurements have been made. It was decided, therefore, to measure by means of the embryonic duck heart method the renal excretion of this glycoside in normal young subjects. The results of this study published herein indicate that digoxin is indeed excreted by man far more rapidly than digitoxin.

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METHODS

Eight normal young male and female subjects received 1.25 mg. of digoxin (Lanoxin®, Burroughs Wellcome) orally in a divided dosage of 0.25 mg. digoxin at five two-hour intervals. Twenty-four hour urine collections were begun immediately following the initial 0.25 mg. of the drug and continued over a period of four days. In addition, the urine was collected for 24 hours on the eighth day after initial ingestion in four of the eight subjects.

Digoxin was extracted from a 5 ml. aliquot of the 24 hour urine with 25 ml. chloroform by partition in glass stoppered test tubes. The phases were cleared by centrifugation; then the aqueous layer was aspirated off. Residual water and the interphase material were removed by filtration of the remaining tube contents through Whatman No. 5 paper into Erlenmeyer flasks (125 ml. with ground stoppers). The extraction tubes and filter paper were thoroughly washed with chloroform. After the extract was evaporated to apparent dryness, the last traces of chloroform fumes were driven off by the addition of alcohol and then the flasks brought to dryness. A standard volume of Tyrode's solution (5 ml.) was added to the flasks which were then shaken for one hour. The digoxin or cardioactive content of this extract was assayed by the embryonic duck heart method (1).

Recoveries of standard amounts of digoxin were made from samples of each subject's urine taken immediately before the initial ingestion of digoxin. The sensitivity of the method permitted the identification and measurement of amounts of digoxin of as little as 0.02 μg. per ml. of urine.

RESULTS

As shown in Table I, the maximal amount of digoxin is excreted during the first 24 hours after the ingestion of 1.25 mg., during which time an average of 169 μg. or 13.5 per cent of the total dose was excreted. A marked decline in the average excretion ensued in the subsequent two days, and on the fourth day three of the seven subjects

TABLE I

The renal excretion of 1.25 mg. digoxin

Subject	Age	Weight	Amount of digoxin in daily urine				
			Day 1	Day 2	Day 3	Day 4	Day 8
		lbs.			*μg.*		
T. I.	32	180	168	120	52		
C. Y. O.	34	135	207	172	88	85	N.D.*
W. H.	32	128	196	187	54	32	N.D.
J. P.	29	180	62	62	65	N.D.*	N.D.
M. S.	32	208	152	152	46	N.D.	
V. M.†	22	108	78	38	28	N.D.	
L. D.†	33	128	270	152	136	81	
E. D.†	32	118	224	150	63	45	N.D.
Average	31	148	169	129	66	61	
S. E. Mean			±23	±17	±11		

* N.D., no digoxin detectable (*i.e.*, less than 25 μg. of digoxin in 24 hour urine volume).
† Female.

examined failed to excrete detectable amounts of digoxin (*i.e.*, less than 25 μg.). None of four subjects tested excreted detectable amounts of the drug on the eighth day after its ingestion.

DISCUSSION

When these results are compared with those obtained on both normal and cardiac subjects given digitoxin (3, 6) it is clear that the human subject excretes a considerably larger fraction of ingested digoxin than of digitoxin, at least during the first 72 hours after administration. Whereas the young subject cannot excrete more than 5 per cent of a given dose of digitoxin in 24 hours or more than 14 per cent in 72 hours, he can excrete approximately 14 and 29 per cent, respectively, of administered digoxin during the same time intervals.

Although we were not able to detect digoxin in the urine of any subject eight days after the drug's ingestion, digitoxin could still be detected in the urine of the majority of subjects 15 days after its administration (3). However, this does not necessarily indicate that the former subjects were not still excreting some digoxin because our method of detection was considerably less sensitive for the presence of digoxin than digitoxin in urine. Thus our subjects could still have been excreting digoxin after the eighth day in daily quantities of less than 25 μg.—our critical endpoint of detection. Nevertheless it seems quite doubtful that the entire amount of digoxin was eliminated via the kidney. Rather it appears that, like digitoxin (3, 4), not only does the human subject eliminate digoxin by excretion of the intact substance and its cardioactive fragment but also probably metabolizes a large fraction of it.

SUMMARY

The renal excretion of digoxin was studied in eight normal young subjects by means of the embryonic duck heart technique. The excretion of this glycoside was found to be approximately twice as rapid as that of digitoxin during the first 72 hours after its administration.

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