

The Effect on Myocardial ^3H -Digoxin of Magnesium Deficiency¹ (35356)

ROBERT H. GOLDMAN, ROBERT E. KLEIGER, ESTHER SCHWEIZER,
AND DONALD C. HARRISON

Cardiology Division, Stanford University School of Medicine, Palo Alto, California 94305

The role of potassium deficiency in producing digitalis toxicity has been appreciated for many years (1). However, the effects of magnesium deficiency on tolerance to digitalis are less well known. It has been shown that chronic depletion of magnesium prolongs the duration of digitalis toxicity (2), while acute depletion of serum magnesium decreases the dose of acetyl strophanthidin needed to produce digitalis toxic arrhythmias (3). The mechanisms by which magnesium deficiency affects the responses of the heart to digitalis are not understood, although it has been suggested that magnesium deficiency may act by decreasing tissue potassium levels (3). The present study investigated the effects of chronic magnesium deficiency on the uptake and retention of ^3H -digoxin by the mouse heart to determine whether magnesium deficiency alters myocardial ^3H -digoxin metabolism, and thereby influences sensitivity to cardiac glycosides.

Materials and Methods. Female Swiss-Webster mice, weighing 20–28 g, were made magnesium-deficient by feeding them a magnesium-deficient diet (4) and distilled water for 15 days. Control animals received the same diet, to which was added MgCl_2 , 2 g/kg of diet. The animals were then given ^3H -digoxin, sp act 105 $\mu\text{Ci}/\text{mg}$, in a dose of 250 $\mu\text{g}/\text{kg}$ of body weight, intraperitoneally. At 1, 3, 6, 18, and 24 hr after injection, groups of mice were sacrificed and their hearts were assayed for ^3H -digoxin (5). In animals not given digoxin, blood samples were obtained from the retinal artery prior to sacrifice for electrolyte determination. These same animals were used for the determina-

tion of myocardial electrolytes. Plasma potassium was determined in duplicate by flame photometry (Model 143, Instrumentation Laboratory, Boston, Mass.). Plasma magnesium and calcium were determined by atomic absorption spectrophotometry (atomic absorption spectrophotometer, Model 290, Perkin-Elmer Corporation, Norwalk, Conn.) (6). Myocardial potassium and magnesium were also determined in duplicate by atomic absorption spectrophotometry after the hearts had been dried to a constant weight *in vacuo* at 140° for 48 hr, wet-ashed in concentrated nitric acid until fully digested, then diluted to volume. Tissue water content was determined by subtracting dry weight of tissue from wet weight, and was found to be the same for both control and magnesium-deficient hearts. Blood urea nitrogen (BUN) was determined by Technicon AutoAnalyzer.

Statistical analyses were performed using the Wilcoxin two-sample rank test (7) for ^3H -digoxin concentration, electrolyte concentration, tissue water content, and BUN.

Results. Figure 1 shows the concentration of ^3H -digoxin (cpm/g of heart) in the hearts of both control and magnesium-deficient mice. At 1 hr, the time of maximal uptake of ^3H -digoxin (8), there was significantly less myocardial ^3H -digoxin in magnesium-deficient animals compared with controls. At 3, 6, 18, and 24 hr, however, there was significantly more ^3H -digoxin in the myocardium of magnesium-deficient animals than in controls (Table I). To determine whether these differences in myocardial ^3H -digoxin concentration were due to differences in absorption of ^3H -digoxin from the peritoneal cavity, a second series of mice were studied. These animals were treated as before, except that they were given the same dose of ^3H -

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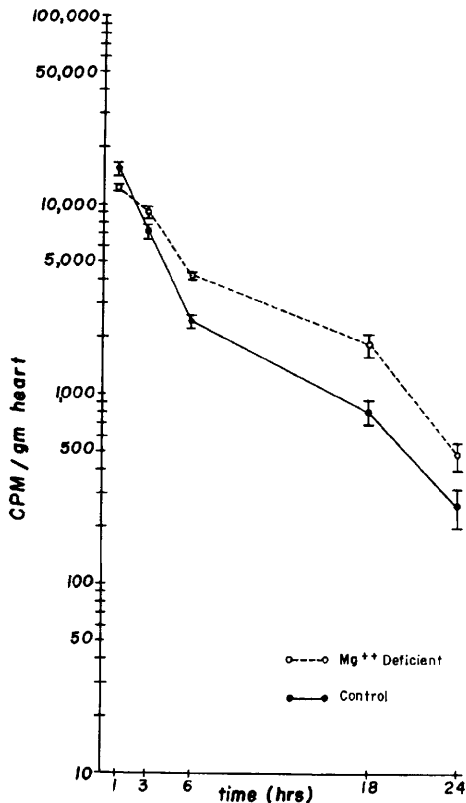


FIG. 1. The time course of decline of myocardial ^3H -digoxin concentration (cpm/g of heart) in mice given ^3H -digoxin: control mice (●); and magnesium-deficient mice (○).

digoxin but of higher sp act: $125 \mu\text{Ci}/\text{mg}$, compared with $105 \mu\text{Ci}/\text{mg}$. These animals were sacrificed only at 1 and 24 hr. Plasma ^3H -digoxin was then measured by the method of Gonzales and Layne (9). At 1 hr, there was no difference in plasma ^3H -digoxin between control and magnesium-deficient animals ($35,693 \pm 1308$ vs $31,401 \pm 2717$

cpm/ml of plasma \pm SE). At 24 hr the control animals had significantly lower plasma ^3H -digoxin than the magnesium-deficient animals (875 ± 51 vs 2016 ± 139 cpm/ml of plasma). At 1 hr, these control hearts also had significantly more ^3H -digoxin than magnesium-deficient hearts ($27,934 \pm 1268$ vs $17,401 \pm 1502$ cpm/g \pm SE), while at 24 hr, hearts of control animals had less ^3H -digoxin than the hearts of magnesium-deficient animals (564 ± 52 vs 702 ± 95 cpm/g \pm SE).

In Table II is shown the plasma concentration of potassium, magnesium, calcium, and BUN, as well as the myocardial concentration of potassium and magnesium for these animals. There was no difference between control and magnesium-deficient animals in plasma concentration of potassium, calcium, or BUN, while plasma magnesium and myocardial potassium and magnesium were significantly lower in magnesium-deficient animals.

Discussion. The mechanism by which chronic magnesium deficiency decreases initial uptake of ^3H -digoxin by the heart is not clear. Several possibilities merit consideration. It is unlikely that altered absorption of ^3H -digoxin from the peritoneal cavity is responsible since plasma ^3H -digoxin levels at one hour were similar in control and magnesium-deficient animals. Altered ^3H -digoxin delivery to the heart due to altered coronary blood flow also appears unlikely since there is no evidence that magnesium deficiency alters coronary blood flow. Decreased ^3H -digoxin uptake secondary to the tissue potassium deficiency produced by magnesium deficiency may be an important

TABLE I. Myocardial ^3H -Digoxin Concentration in Control and Magnesium-Deficient Mice.

Time (hr)	Control		Magnesium-deficient		p value ^b
	(cpm/g of heart \pm SE)	No. ^a	(cpm/g of heart \pm SE)	No. ^a	
1	$15,384 \pm 1306$	8	$12,266 \pm 486$	9	0.001
3	7122 ± 678	8	9078 ± 668	9	0.025
6	2398 ± 194	8	4232 ± 154	9	<0.001
18	812 ± 123	8	1839 ± 253	9	0.005
24	259 ± 64	14	484 ± 81	15	<0.001

^a Number of experimental animals in each group.

^b Significance of difference between control and magnesium-deficient animals.

TABLE II. Plasma and Myocardial Electrolyte Concentration in Control and Magnesium-Deficient Mice.

	Control		Magnesium-deficient		p value ^b
	(mEq/liter ± SE)	No. ^a	(mEq/liter ± SE)	No. ^a	
1. Plasma					
K ⁺	4.50 ± 0.17	6	4.43 ± 0.18	6	NS
Mg ²⁺	2.43 ± 0.14	4	1.24 ± 0.07	5	0.01
Ca ²⁺	10.96 ± 0.23	4	10.45 ± 0.28	5	NS
BUN	30.3 ± 2.0 mg/100 ml	5	30.5 ± 2.4 mg/100 ml	5	NS
	(mEq/100 g of dry wt ± SE)		(mEq/100 g of dry wt ± SE)		
2. Heart					
K ⁺	35.23 ± 0.86	7	31.16 ± 0.73	9	0.005
Mg ²⁺	10.11 ± 0.28	8	8.63 ± 0.39	9	0.001

^a Number of experimental animals in each group.

^b Significance of difference between control and magnesium-deficient animals.

factor, since it has been shown that potassium deficiency decreases the uptake of ³H-digoxin in the rat heart (8). Still another explanation is suggested by studies showing that magnesium deficiency inhibits digoxin binding to ATP-ase *in vitro* (10).

Twenty-four hr after injection, magnesium-deficient mice had higher myocardial and plasma ³H-digoxin levels than controls. Although decreased renal excretion of ³H-digoxin appears an unlikely factor since BUN was normal, this possibility cannot be excluded without direct measurement of urinary ³H-digoxin excretion. Moreover, the tissue potassium deficiency caused by magnesium deficiency may itself be responsible for both the decreased initial uptake of digoxin and the subsequent increased retention of ³H-digoxin in the myocardium and plasma (5, 8). Further experiments using magnesium-deficient mice with normal tissue potassium levels are necessary to differentiate the direct effects of magnesium deficiency on ³H-digoxin metabolism from those secondary to magnesium deficiency-induced potassium deficiency.

Although the mechanism by which magnesium deficiency alters ³H-digoxin metabolism is not clear, these biochemical studies may explain the increased sensitivity to digitalis seen in hypomagnesemic patients receiving digitalis chronically, since their myocardium would be expected to retain more of a daily dose of digitalis than normal patients.

Summary. The hearts of magnesium-

deficient mice accumulate less ³H-digoxin 1 hr after intraperitoneal injection than do controls. At 3, 6, 18, and 24 hr, magnesium-deficient mice retained more ³H-digoxin than controls. The difference in the initial uptake of ³H-digoxin between control and magnesium-deficient animals is not due to different blood ³H-digoxin levels. The role of magnesium deficiency-induced potassium deficiency in altering myocardial ³H-digoxin metabolism is discussed.

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