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The Turnover of Magnesium in Control Subjects and in Patients With Idiopathic Cardiomyopathy and Congestive Heart Failure Studied With Magnesium-28[1]

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The pharmacologic properties of magnesium have been studied (1-3) although the nutritional and clinical importance and the biochemical role of magnesium, particularly as an activator in enzyme systems, were intensively investigated only recently (4-11). Information of the kinetics of magnesium in the human body is of importance. An average adult has about 25 g of magnesium in his body (12). The average American daily diet contains about 300 mg of magnesium with the accepted daily requirement being 250 mg (13-14). However, precise knowledge of the daily rate of turnover of magnesium in the body is not known. Earlier data, derived from either nonisotope techniques or by radioisotope studies, are all overestimations because of the loading effect of the dose of ^{24}Mg administered. The present study was carried out with ^{28}Mg of very high specific activity[3] to minimize loading.

MATERIALS AND METHODS

This study was performed in conjunction with long term balance studies of Mg in which ^{28}Mg and H^3OH were employed as tracers. Six subjects, two controls and four patients with idiopathic cardiomyopathy and congestive heart failure, were observed. The clinical information is summarized in Table I. All subjects were kept at bed rest except for bathroom privileges and were fed identical diets containing 200 to 300 mg of magnesium per day. Each meal was

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[3]Specific activity was approximately 20 mC. ^{28}Mg-^{28}Al per gram of Mg, about 20 times that of the ^{28}Mg used previously. It was obtained from Hot Laboratory Division, Brookhaven National Laboratory, Upton, Long Island, N. Y.

weighed before and after serving, and the actual intake of magnesium was determined from standard tables of foodstuffs. All excreta were collected and venous blood was sampled at least once a day.

The doses of ^{28}Mg and its stable carrier are indicated in Table I. The tracer was administered intravenously by rapid injection (less than 20 seconds) except in Patient A.T. in whom ^{28}Mg in 150 ml of five per cent dextrose was infused intravenously at a constant rate over a period of six minutes. Urine was sampled by means of an indwelling catheter at frequent intervals for the first three to four hours. Later, voided urine was collected. The follow-up period was 42 to 70 hours for the ^{28}Mg. In control Subject B.S. and Subject M.M., an oral dose of ^{28}Mg was administered 12 days after the intravenous dose. Blood, urine and stool were collected for comparison.

Magnesium-28 was assayed for beta emission with a gas-flow counter (Baird-Atomic). Urine and plasma were prepared on planchets by methods previously described (15). Homogenized stool specimens were counted with a thin layer on the planchets. Total magnesium was determined with flame photometry (Zeiss PMQII with double monochromator) according to the method described by MacIntyre (16) except that acid digestion (17) was used for the stools.

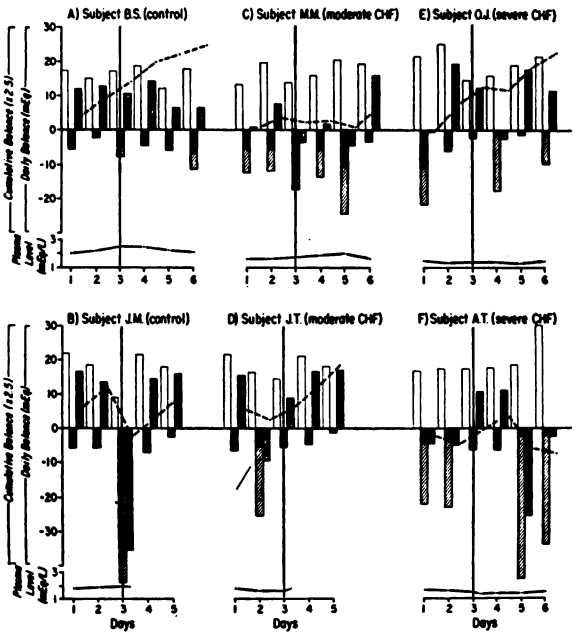

Fig. 1. Daily balance and plasma level of Mg for the two control subjects and four subjects with idiopathic cardiomyopathy and chronic congestive heart failure. The Mg intake is indicated by the blank columns above the baseline and ouput by columns below the baseline. Output in the urine is indicated by black columns and in the stool by obliquely striped columns. The daily Mg balance is indicated by strippled columns and cumulative balance by interrupted lines. The vertical line at the third day denotes the time at which the intravenous dose of ^{28}Mg was administered.

TABLE I

CLINICAL DATA ON THE 6 SUBJECTS STUDIED

Subject	*Age*	*Sex*	*Weight (kg)*	*Diagnosis*	*Therapy*	*I.V. dose*		*Oral dose*	
						^{28}Mg (μC)	Total Mg (meq)	^{28}Mg (μC)	Total Mg (meq)
				Controls					
BS	44	F	68	Psychoneurosis	phenobarbital	145	1	75	0.5
JM	48	M	64	Cardiomyopathy without CHF		155	1		
				Patients with Idiopathic Cardiomyopathy and Congestive Heart Failure					
MM	49	F	70	CHF moderate; diabetes mellitus	digitalis insulin belladonna	141	1	75	0.5
JT	55	M	89	CHF moderate	digitalis quinidine phenobarbital	160	1		
OJ	56	F	70	CHF severe	digitalis	151	1		
AT	54	M	89	CHF severe	digitalis phenobarbital	135	2		

TABLE II

DATA FOR DAILY TURNOVER OF Mg (MEQ)

	Control Subjects			*Patients with CHF*				
	BS		*JM*	*MM*		*JT*	*OJ*	*AT*
Average daily intake	16.3		17.7	16.8		18.2	19.3	19.8
Average daily fecal excretion†	1.1		7.9	7.8		4.1	6.2	17.9
Absorption from g-i tract								
calculated from fecal excretion (average daily intake—average daily fecal excretion)	15.2		9.8	9.0		14.1	13.1	1.9*
calculated from oral ^{28}Mg study (intake × 1% fecal excretion)		13.0			9.6			
Average daily urinary excretion	4.8	4.8	4.9	5.2	5.2	4.4	3.6	4.8
contributed by newly absorbed (amount absorbed × % urinary excretion of ^{28}Mg in 24 hours from I.V. ^{28}Mg study)	< 0.9	< 0.8	< 0.4	< 0.6	< 0.7	< 0.7	< 0.4	<0.1
contributed by magnesium pool in the body	> 3.9	> 4.0	>4.5	> 4.6	4.5	> 3.7	> 3.2	>4.7
Fate of newly absorbed magnesium								
% excreted in 24 hours	< 6.2		< 4.1	< 6.8		< 5.3	< 3.1	< 3.9
% excreted in the next day or two	< 4.5		< 3.2	< 3.2		< 1.3	< 0.4	< 1.8
% excreted slowly	>89.3		>92.7	>90.0		>93.4	>96.5	>94.3

*Subject AT had frequent bowel movements during the period.

†Secretion of endogenous Mg, less than 0.7% of daily intake in three days, was not included. See text and Figure 2.

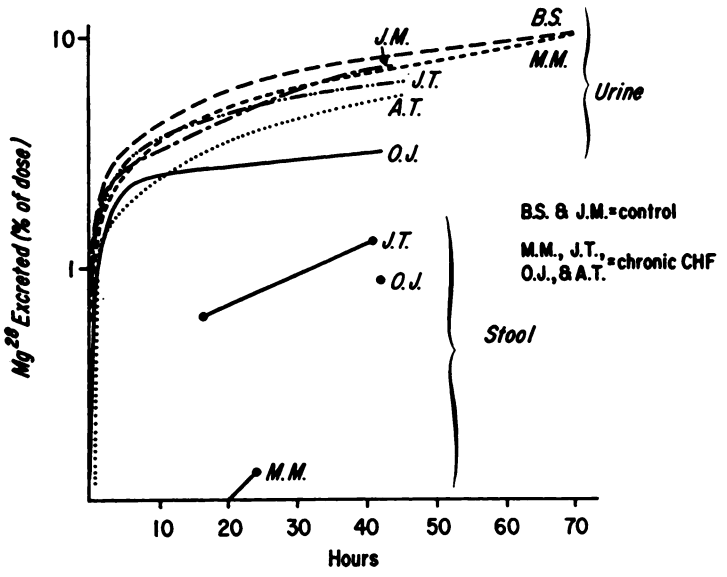

Fig. 2. Cumulative excretion of ^{28}Mg in the urine and stool following intravenous administration of the tracer in six subjects (2 controls; 4 with idiopathic cardiomyopathy and chronic congestive heart failure). Stools were not collected in Subjects BS and JM. The cumulative excretion of ^{28}Mg in stool of Subject AT was less than 0.1% in three days.

RESULTS

1. *Daily Balance and Plasma Level of Mg:* The daily intake, output, balance and plasma level of Mg for the two days before and three days after the intravenous administration of ^{28}Mg in the six subjects are shown in Figure 1. The intravenous administration of ^{28}Mg did not change the daily urinary excretion and plasma level of Mg. The average daily intake and urinary output of Mg were quite similar among the six subjects as shown in Table II. However, the fecal excretion and the cumulative balance of Mg varied greatly. With the exception of Patient A.T., all subjects were in positive Mg balance as measured.

2. *Excretion of ^{28}Mg Following Intravenous Administration:* Cumulative excretion of ^{28}Mg in the six subjects following intravenous administration of ^{28}Mg is shown in Figure 2. During the period of observation, the total excretion in the urine was 3.1% to 10.7% of the dose. That in the stool was 0.1% to 1.4% of the dose.

The curve for the time course of the rate of urinary excretion of the ^{28}Mg in a representative Patient, Subject B.S., is shown in Figure 3. The curves for all of the patients were analyzed exponentially by visual fitting (18) and are represented by the following equations for each subject;

Subject B.S. $\frac{dU}{dt} = e^{-0.4278t}\,0.126e^{-0.077t}\,0.106e^{-0.00236t}$

Subject J.M. $\frac{dU}{dt} = e^{-0.693t}\,0.2e^{-0.139t}\,0.11e^{-0.00173t}$

Subject M.M $\frac{dU}{dt} = 0.7e^{-0.417t}\,0.3e^{-0.094t}\,0.1e^{-0.00136t}$

Subject J.T. $\frac{dU}{dt} = 0.6e^{-0.35t}\,0.3e^{-0.154t}\,0.07e^{-0.00133t}$

Subject O.J. $\frac{dU}{dt} = 0.9e^{-0.693t}\,0.26e^{-0.18t}\,0.02e^{-0.00108t}$

Subject A.T. $\frac{dU}{dt} = 0.5e^{-0.693t}\,0.15e^{-0.117t}\,0.08e^{-0.00108t}$

where $\frac{dU}{dt}$ is the instantaneous rate of urinary excretion at any time, t, expressed in per cent of the administered dose per hour. From the equations the total amount excreted in the urine in the observation period and in the first 24 hours was calculated by integration of the respective curves (Fig. 3, Table III). The calculated amount of urinary excretion for the period of observation was very close to that obtained directly from the ^{28}Mg accumulated in the urine (Table III).

3. *Excretion of ^{28}Mg Following Oral Administration:* The specific activity of ^{28}Mg in the plasma following an oral dose of ^{28}Mg was too low for significant counting. The specific activity of ^{28}Mg in the urine for control Subject B.S. and Subject M.M. are shown in Figure 4. The highest level was reached at 12 to 14 hours after administration of the tracer. In control Subject B.S. and Subject M.M. the fecal excretion followed for six days were 20.3% and 42.7%, respectively, of the dose administered, while the urinary excretions in 40 hours were 4.2% and 1.6%, respectively, of the dose administered. The recovery in the urine was not complete since ^{28}Mg still remained significantly high in the urine at 40 hours.

DISCUSSION

Previous studies have shown that the secretion of endogenous magnesium into the gastrointestinal tract is negligible (19-21). This study showed that following intravenous administration of ^{28}Mg, less than 1.4% of the dose was recovered in the stool in two to three days. Patient A.T. who had frequent bowel movements excreted more than 90% of the ingested ^{24}Mg, but his fecal recovery of ^{28}Mg was still less than 0.1% of the intravenous dose. If one-half of the daily intake of magnesium is absorbed into the blood and the absorbed magnesium is

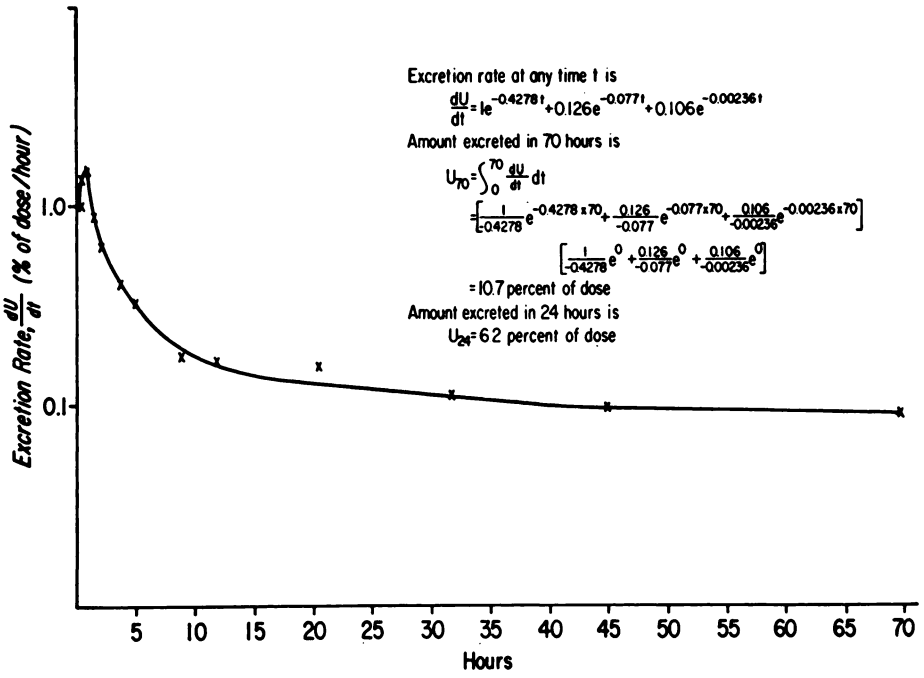

Fig. 3. Time course of the rate of urinary excretion following intravenous administration of ^{28}Mg in a representative control subject, Subject BS. The amount excreted in the observation period and in the first 24 hours is calculated.

TABLE III
URINARY EXCRETION OF ^{28}MG (% OF DOSE) FOLLOWING INTRAVENOUS ADMINISTRATION

	Excretion during observation period			
Subject	*Duration of observation (hours)*	*Measured amount*	*Calculated* amount*	*Calculated* amount for first 24 hours*
		Control Subjects		
BS	70	10.7	10.7	6.2
JM	44	7.6	7.3	4.1
		Patients with Idiopathic Cardiomyopathy and CHF		
MM	70	10.5	10.0	6.8
JT	45	6.4	6.6	5.3
OJ	42	3.1	3.5	3.1
AT	45	5.7	5.7	3.9

*Calculation is made by integration of the exponential equations for excretion rate-time course curves. Consult text and Figure 3 for details.

secreted into the gastrointestinal tract in the same manner as the intravenously administered ^{28}Mg, the endogenous secretion of the ingested magnesium would be less than 0.7% of the daily intake in two to three days. Therefore, the amount of magnesium absorbed from the gastrointestinal tract can be calculated as the difference between the average daily intake and the average fecal excretion.

A study of the kinetics and metabolic behavior of the absorbed magnesium traced with oral ^{28}Mg is made difficult by the low plasma level of the tracer. Intravenously administered ^{28}Mg can be studied as a substitute for the absorbed magnesium only if the loading effect from the carrier Mg in the intravenous dose is minimal. Lack of loading effect following the intravenous doses used in this study is manifested directly by the constancy of the plasma level and the urinary output of Mg. These profiles, however, may not be sensitive enough to reflect changes that could have occurred. If the intravenous dose (1 meq of Mg carrier given in 20 seconds) produced no greater *loading* effect on the kidneys for excretion than normally seen at the postprandial state, the per cent excretion of ^{28}Mg following intravenous administration should be no greater than the percent excretion of the absorbed ^{28}Mg following oral administration. Two subjects who had both oral and intravenous administrations served for comparison, assuming that the metabolic conditions during the interval did not change significantly. Following oral administration the urinary excretion of ^{28}Mg in 40 hours was 4.2% and 1.6% of the dose, or 5.3% and 2.7% of that absorbed by control Subject B.S. and Subject M.M., respectively. The urinary excretions of ^{28}Mg following intravenous dose, integrated over 40 hours, were 8.1% and 8.8% for control Subject B.S. and Subject M.M., respectively. Although the values for urinary excretion following

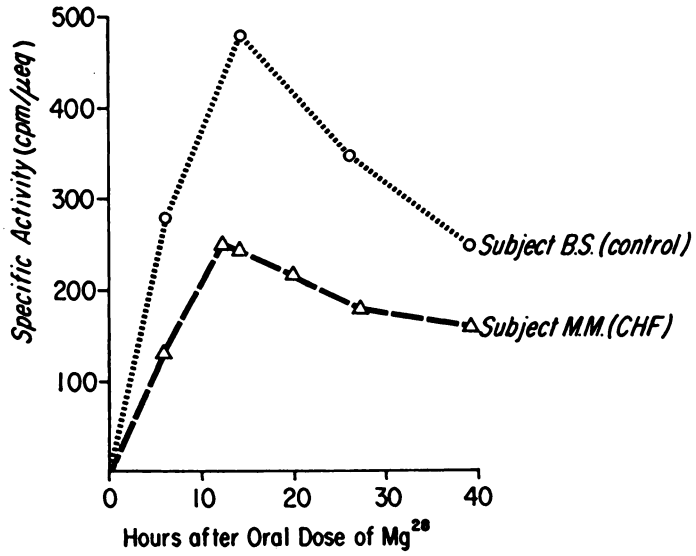

Fig. 4. Specific activity of ^{28}Mg in the urine following an oral dose in control Subject BS and Subject MM with idiopathic cardiomyopathy and chronic congestive heart failure.

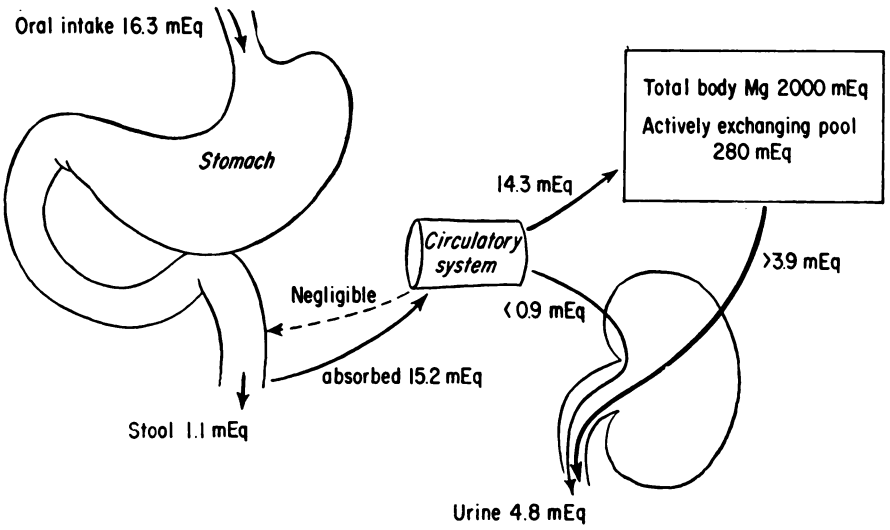

Fig. 5. Diagram of daily turnover of magnesium in a representative control subject, Subject BS. The amount of magnesium absorbed was obtained from the difference of the average daily intake and the average daily fecal excretion. The amount of magnesium newly absorbed from the diet and excreted in the urine was calculated from the data obtained from the study of the intravenously administered ^{28}Mg. Consult text and Table II for details.

intravenous dose in this study are much smaller than those reported previously (40-50% in 48 hours) (21), they are still greater than those calculated from the oral dose. This suggests that the carrier in the intravenous dose, though small in amount, still imposed some additional *loading* effect than normally seen at the postprandial state. Therefore, the calculated amount of urinary magnesium contributed by newly absorbed magnesium, based on the intravenous ^{28}Mg study, is slightly over-estimated (Table II).

With the exception of Subject O.J., the average daily urinary excretion of Mg in all of the subjects was about five meq. This is essentially the low normal limits reported elsewhere (14,22,23). Since all subjects except Subject A.T. were in positive magnesium balance and the gastrointestinal absorption was 79.7% and 57.3% of the oral dose administered in two representative subjects, the low rate of urinary excretion of magnesium must not be the result of impaired gastrointestinal absorption. Low magnesium and previous use of diuretics in subjects with congestive heart failure probably explain this in part. Since the fecal excretion, and hence the amount absorbed, varied greatly, the relatively uniform urinary excretion must be maintained primarily by regulating mechanisms concerned with the magnesium pool of the body. This is also evidenced by the great percentage of the urinary magnesium contributed by the magnesium pool (Table II).

Magnesium turnover for the six subjects were calculated as shown in Table II and Figure 5. With low normal magnesium intake, the daily urinary output is about one-fifth to one-fourth of the daily intake. Of the daily urinary output, less

than 18% is derived from the newly absorbed magnesium, whereas, the remainder is derived from the magnesium pool of the body. Therefore, urinary magnesium contributed by newly absorbed magnesium is only 3.6-4.5% of the daily intake. Aikawa's report (20) that maximal 24-hour urinary excretion is 6.2% of the oral dose of ^{28}Mg is about the same as that found in this study (Table II). The major part (90% or more) of the absorbed magnesium is excreted slowly. Patients with congestive heart failure had even slower rates of excretion as shown by the coefficients of the third terms of the exponential equations. Fecal magnesium represents that unabsorbed with endogenous secretion being negligible. The total body magnesium determined chemically was reported to be 30 meq/kg of body weight (12), and the actively exchanging pool of magnesium was 3.0-4.3 meq/kg of body weight (25).

ABSTRACT

Daily turnover of magnesium in control subjects and in patients with idiopathic cardiomyopathy and congestive heart failure was studied with ^{28}Mg of high specific activity, administered by both oral and intravenous routes under controlled metabolic conditions. Gastrointestinal absorption of magnesium varied from 53% to 93% of the daily intake. Of the absorbed magnesium less than seven per cent was excreted in the urine in the first 24 hours, and less than 10% in two to three days. More than 90% of the absorbed magnesium was excreted in the urine very slowly. The patients with congestive heart failure had even slower rates of excretion. The magnesium in the urine was derived largely from the magnesium pool of the body, the newly absorbed magnesium being responsible for less than 18% of the daily urinary excretion. Endogenous secretion of magnesium into the fluids of the gastrointestinal tract was negligible.

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