Magnesium metabolism in human beings: studies with Mg^{28} [1]

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AIKAWA, JERRY K., GERALD S. GORDON AND ELOISE L. RHOADES. *Magnesium metabolism in human beings: studies with Mg^{28}.* J. Appl. Physiol. 15(3): 503–507. 1960.—Mg^{28} was used to explore the kinetics of magnesium distribution in 9 normal individuals and in 16 patients with various diseases. When Mg^{28} was given in 12–30 mEq of stable magnesium intravenously, plasma disappearance was rapid within the first several hours. In normal subjects a mean of 19.8% of the injected radioactivity was accounted for in the urine within 24 hours. Fecal excretion was negligible, although equilibration of Mg^{28} in bile occurred within 18 hours. The specific activities of plasma and urine stabilized by the 18th hour, and showed only a gradual decrease thereafter. Exchangeable magnesium contents in normal subjects ranged between 2.6 and 5.3 mEq/kg of body weight—less than 16% of the estimated total body content of magnesium. Mg^{28} exchanged very slowly with the stable ion in bone, muscle and erythrocytes. The results in patients with diabetes mellitus and hepatic diseases showed no striking differences from those obtained in normal subjects.

MAGNESIUM, an intracellular cation present in quantities second only to potassium, is of considerable importance in living organisms (1). It is known to activate many enzymes (2), to play an essential role in neuromuscular function and to be an important constituent of bone. Until recent years, studies on magnesium metabolism have been hampered by technologic problems: chemical determinations of magnesium in biologic material were difficult, and no suitable isotope was available for dynamic studies. Mg^{28}, a radioactive isotope discovered in 1953 by Sheline and Johnson (3), has recently become available in quantities and with a specific activity high enough for observations to be made in human subjects without the danger of chemical toxicity.

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In the present study Mg^{28} (supplied by Brookhaven National Laboratory on allocation from U.S. Atomic Energy Commission) was used to explore the kinetics of magnesium distribution in normal subjects and in patients with various diseases. The results of similar studies in rabbits, and of a study on the gastrointestinal absorption of Mg^{28} in man and in rabbits have been reported previously (4–6).

MATERIALS AND METHODS

A total of 27 studies were performed on 25 hospitalized subjects (17 males and 8 females) between the ages of 12 and 76 years (table 1). No attempt was made to control the patient's caloric or fluid intake during the period of observations; none, however, received any medication containing magnesium.

Radiomagnesium (Mg^{28}) was prepared in a manner described previously (6) and administered intravenously in 250–350 ml of 5% dextrose in water. The average amount of carrier magnesium administered was 13.5 mEq together with about 10^7 c.p.m. of radioactivity.

Urine samples and samples of blood from the brachial vein were collected at intervals over the next 24 hours. In a few instances, blood samples were collected for as long as 37 hours and urine samples for 67 hours. All samples were collected in chemically clean glassware, and the blood samples were drawn into heparinized syringes.

In addition to the routine sampling performed on all patients, the following additional specimens were obtained in selected cases: *a*) blood samples taken simultaneously from the brachial artery and vein during and after infusion in three patients; *b*) samples of liver, muscle, fat, skin, appendix, bone or bile from four patients; and *c*) complete 72-hour stool collection in one patient. In three patients, surface monitoring was performed with a directional scintillation counter attached to a recording counting rate meter.

Serum and urine magnesium determinations were performed by a modification (7) of the molybdivanadate method for phosphate (8).

Samples of serum, urine and tissue were assayed for

TABLE 1. *Summary of Results of Mg^{28} Studies in Human Subjects*

Case No.	Age	Sex	Wt.	Dose of Mg	Clinical Diagnosis	Infus. Time	Serum Mg Concen.			Renal Excretion				Exchangeable Mg^e		
							B.L.[a]	Max.[b]	Min.[c]	Of Mg^{28}		Of Mg^{24}		Plasma	Urine	Mean
										0-8′	0-24′	0-8′	0-24′			
			kg	*mEq*		*min.*	*mEq/l.*							*mEq*		*mEq/kg*
1	17	F	49.5	14.0	Normal	6	1.68	4.11	1.29	24.3	26.7	9.5	13.5	125	135	2.6
2	18	M	100.7	30.0	Normal	83	1.51	2.27	1.34	18.9	20.6	18.1	22.4	270	309	2.9
3	49	M	65.2	97.0	Normal	75	1.32	5.49	1.91	42.4	45.0[f]	70.4	79.0[f]			
				16.0		60	1.91	2.61	1.21	26.2	30.7	20.6	31.6		186	2.8
4	21	M	71.8	13.0	Normal	60	1.56	2.08	1.36	18.7	20.2	5.3	6.0	397	370	5.3
5	54	F	52.3	14.5	Normal except for cholecystitis	51	1.61	2.35	1.53	19.5	20.8	6.0	10.6	146	135	2.7
6	47	M	67.5	20.0	Normal	19	1.64	3.15	1.54	16.6	19.6	1.9		229	259	3.6
7	36	M	56.6	12.0	Normal	16	2.10	2.70	1.90	16.2	25.3	15.6	36.0	222	262	4.3
8	52	M	69.8	12.0	Normal	13	1.70	2.50	1.80	9.7	11.9	6.1	10.5	255	249	3.6
9	36	M	63.2	12.0	Normal	17	1.60	2.50	1.60	17.7	20.7	17.7	24.4	181	217	3.1
10	72	M	74.1	18.7	Diabetes mellitus	23		2.22	1.55	8.9	14.2	1.1	8.2	194	177	2.5
11	22	M	45.5	10.0	Diabetes mellitus	16	1.27	1.78	1.29	11.6	13.6	8.4	12.4	268	241	5.6
			48.6	8.0		18		1.50	1.50	12.0	17.4	16.3	23.7	254	247	5.2
12	50	F	56.4	10.0	Diabetes mellitus	5	1.52	1.99	1.45	19.2	23.4	9.5	18.0	222	198	3.7
13	12	M	33.6	7.5	Diabetes mellitus	10	1.41		1.39	19.9	22.4	19.9	22.4	157	161	4.7
14	76	M	53.2	14.0	Ca pancreas, biliary obst.	60	2.56	2.64	1.75	7.0	12.5	4.1	10.4	156	147	3.8
15	52	F	53.6	20.0	Cirrhosis	20	1.13	2.80	1.51	43.7	55.4	7.3	14.9	27	39	0.1
16	21	M	72.7	13.0	Hepatitis	20		2.31	1.64	22.6	26.2	22.1	32.0	234	239	3.3
17	62	F	66.8	10.0	Hepatitis	8	1.53	1.93	1.37	9.4	12.6	6.2	10.3	93	105	1.5
18	43	F	67.4	18.7	Hepatitis	19	1.27	2.01	1.32	11.3	12.6	8.7	17.7	209	208	3.1
19	46	F	60.0	10.0	Cushing's	7	1.90	2.67	1.90	14.6	17.8	10.9	14.8	181	176	3.0
20	16	M	61.4	8.0	Leukemia	18	1.92	2.24	1.83	9.6	12.2	7.0	27.5	320	342	5.4
21	50	M	113.2	12.0	Pickwickian	25	1.41	2.10	1.58	9.5	11.5	8.2	15.5	337	314	2.9
22	23	F	54.1	14.0	Epilepsy	5	1.10	3.18	0.72	24.3	30.0	14.8	25.5	146	175	3.0
23	15	M	46.8	13.7	Hodgkin's	50	1.07	1.74	0.68	20.8	23.9	12.4	18.8	168	194	3.9
24	17	M	57.3	13.7	Renal tuberculosis	34	1.30	1.96	1.09	20.5	26.1	12.8	21.4	250	227	4.2
25	40	M	89.5	28.0	Hypertensive cardiovasc. dis.	42	1.25	2.25	1.38	9.4	11.7	15.6	25.3	422	448	4.9

[a] Value before infusion of Mg^{28}. [b] Maximum plasma Mg concentrations were always observed at the end of an infusion of Mg^{28}. [c] Minimum values observed within 34–37 hours after completion of infusion of Mg^{28}. [d] Expressed as % of Mg^{28} administered intravenously. [e] Values calculated from specific activities of plasma and urine obtained 24 hours after completion of Mg^{28} infusion. [f] Cumulative values from 0 to 14 hours.

gamma ray activity with a Nuclear model DS-3 well scintillation counter connected to a Tracerlab Superscaler. A total of at least 10,000 counts were made on each sample. All determinations were corrected for physical decay.

For calculation of specific activity: specific activity of urine, serum, bile and tissue specimens $= \frac{\text{c.p.m./ml}}{\text{mEq/l.}}$

$$\text{Relative specific activity} = \frac{\text{specific activity of tissue}}{\text{specific activity of serum}}$$

The exchangeable magnesium content was determined by use of the usual formula employed for calculation of exchangeable electrolyte content (6).

RESULTS

Studies in Normal Subjects

Ten studies were performed in nine normal subjects. From 12 to 30 mEq of tagged magnesium were given intravenously over a period of 6–90 minutes. Rapid infusion produced a sensation of burning along the course of the brachial vein up to the shoulder. One patient not in this group (*case 22*) experienced a sensation of generalized heat when a concentrated solution of magnesium was administered very rapidly; the serum magnesium concentration at this time was 3.18 mEq/l. One subject (*case 3*) was initially given, over a period of 75 minutes, 97 mEq of magnesium in 1000 ml of a 5% solution of dextrose in water. Toward the end of the infusion, coincident with the insertion of an arterial needle, extreme drowsiness, tachycardia and hypotension developed. The serum magnesium level at the time of this reaction was 5.5 mEq/l.

The mean serum magnesium concentration prior to the administration of magnesium was 1.64 mEq/l (table 1). At the end of the magnesium infusions, the serum concentrations ranged between 2.3 and 5.5 mEq/l. In seven of nine instances, subsequent values for serum magnesium fell below the base-line values, usually between 17 and 35 hours after completion of the injections;

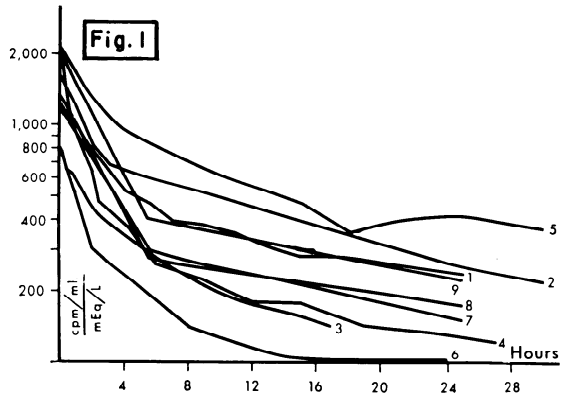

FIG. 1. Specific activities of plasma specimens in normal subjects given Mg^{28} intravenously.

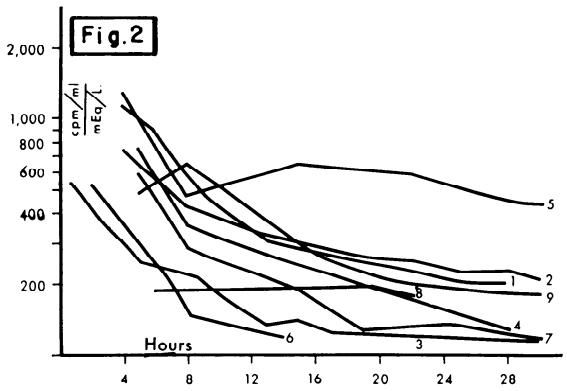

FIG. 2. Specific activities of urine specimens in normal subjects given Mg^{28} intravenously.

one subject (*case 4*), however, showed the lowest value at 90 minutes.

Plasma disappearance of Mg^{28}. The plasma disappearance curves of the nine normal subjects were similar in appearance, showing a rapid initial decrease in concentration for the first 6–8 hours, followed by a slower decline which extended through at least 30 hours. In *case 3* an infusion of 97 mEq of magnesium was given 14 hours before the second infusion of 16 mEq; the second clearance curve was similar to those of the other subjects not given a prior infusion.

The volume of fluid available for dilution of the infused Mg^{28} was calculated from the plasma concentrations of radioactivity. Between 1.25 and 4.75 hours (mean = 3.5 hours) after completion of the intravenous infusions, the radiomagnesium space exceeded the calculated volume of total body water.

Renal excretion. When 12–30 mEq of magnesium were given, 9.7%–26.2% (mean = 19.8%) of the infused radioactivity was recovered in the urine within 8 hours, and 11.9%–30.7% (mean = 21.8%) was recovered within 24 hours. In the subject who received 97 mEq of magnesium (*case 3*), 42.4% was recovered within 8 hours.

In the 24-hour period after administration of the radioactive material, renal excretion of stable magnesium (Mg^{24}) approached or exceeded the amount of magnesium given intravenously. The lowest excretion value (6 mEq) was found in *case 4*, the subject with the highest value of exchangeable magnesium content (5.3 mEq/kg). The subject given 97 mEq of magnesium (*case 3*) excreted 45.0% of the injected radioactivity and 79.4 mEq of stable magnesium within 14 hours.

Specific activity. The results of serial determinations of the specific activity of plasma and urine samples in normal subjects are shown graphically in figures 1 and 2. The curves are in general similar to the configurations obtained for the plasma disappearance of Mg^{28}. Specific activities fluctuated less in plasma than in urine. The specific activities decreased gradually in both urine and plasma after 18 hours.

Exchangeable magnesium content. Values calculated from the urine obtained at 24 hours agreed rather closely with those calculated from plasma; the range in the normal subjects was 2.6–5.3 mEq/kg of body weight, with a mean of 3.4 mEq/kg.

Other studies in normal subjects. In three patients (*cases 2, 3* and *4*) serial blood specimens were obtained simultaneously from the brachial artery and vein during the infusion and for 2.5 hours after completion of the infusion of Mg^{28}. No significant differences were noted in the concentrations of radioactivity from the two sources.

Fecal excretion. In *case 4*, 0.62% of the radioactivity administered intravenously was recovered in the stool within 24 hours; an additional 1.17% was recovered in the next 48 hours.

External survey. In two subjects serial external surveys of radioactivity over the entire body were carried out. In one subject (*case 6*) the maximal distribution of radioactivity at the end of infusion was over the right upper quadrant of the abdomen. In the other subject so studied (*case 4*) the highest counting rates at the end of the infusion were found anteriorly over the liver and the kidneys. Three hours later, the highest distributions were at the femoral triangular areas; at 9 hours, the radioactivity was the same over the epigastrium, the umbilicus, and the suprapubic and femoral triangular areas. At 24 hours, highest counting rates were detected over the epigastrium and umbilical areas, while radioactivity over the femoral triangles had decreased. Radioactivity over the long bones and skull was negligible.

Tissue biopsy studies. An elective cholecystectomy and an incidental appendectomy were performed on one subject (*case 5*) 9 hours after the infusion of Mg^{28}. Specimens of liver, periappendiceal fat and appendix were obtained at operation, and serial plasma and bile specimens were collected postoperatively. The specific activities of serum and bile are given in table 2. The relative specific activity in bile reached unity at 18 hours. At 9 hours the concentration of Mg^{28} in the serum was 1032 c.p.m/ml; in the liver, 8453 c.p.m/gm (wet weight) of tissue; in the appendix, 4209 c.p.m/gm; in fat, 608 c.p.m/gm.

Studies in Patients With Diseases

Diabetes mellitus (cases 10–13). Five studies were performed in four patients with diabetes mellitus. One pa-

TABLE 2. *Specific Activities of Plasma and Bile in Patient Given 14.5 mEq Mg Intravenously*

Time After Injection of Mg^{28}, hr.	Specific Activity		Relative Specific Activity Bile/Serum
	Plasma	Bile	
9	670	154	0.23
12	557	522	0.94
15	475	434	0.91
18	356	384	1.08
21	395	462	1.17
26.5	399	330	0.83
30	369	434	1.18

tient (*case 11*), during acidosis and coma, had a low serum magnesium value of 1.27 mEq/l. The plasma clearance curves observed in this subject during acidosis and coma and a week later were similar.

The mean values for cumulative renal excretion of radioactivity at 8 hours (14.2%) and 24 hours (18.2%) were slightly lower than the respective mean values observed in normal subjects. In four of five instances the urinary excretion of stable magnesium during the first 24 hours exceeded the amount of Mg^{28} given intravenously.

The lowest value for exchangeable magnesium content in this group (2.5 mEq/kg) was found in the subject (*case 10*) who showed the flattest Mg^{28} plasma disappearance curve and the most rapid attainment of stable specific activities in urine and plasma. The highest value (5.6 mEq/kg) was in the diabetic patient studied during acidosis and coma (*case 11*).

One subject (*case 10*) had gangrene of the right leg. Amputation was performed below the knee 10 hours after an intravenous infusion of Mg^{28}. Samples of the fibula, tibia, tibial bone marrow, skin, muscle and subcutaneous connective tissue were assayed for radioactivity content and magnesium content. Comparison of the specific activities of the tissues showed that at 10 hours the injected Mg^{28} had not reached equilibrium with the magnesium in any of the tissues studied. The fibula and tibia showed the lowest relative specific activities, with values of 0.007 and 0.003, respectively.

Hepatic diseases (*cases 14–18*). Five patients with hepatic diseases were studied. Initial serum magnesium values were very low in two patients (*cases 15* and *18*).

Mg^{28} plasma clearance curves and urine and serum specific activities were no different from those observed in normal subjects. In two patients (*cases 14* and *17*) urinary excretion of radioactivity was low during the first 8 hours, but within the normal range at 24 hours. The urinary excretion of stable magnesium during this period was within the range found in normal subjects. One patient (*case 15*) had a very high 24-hour urinary excretion of Mg^{28} (55%). This same patient, who died 6 weeks later in hepatic coma, showed the lowest exchangeable magnesium content found in this study (0.1 mEq/kg), as well as a low initial plasma magnesium concentration. Another patient (*case 17*) had an exchangeable magnesium value of 1.5 mEq/kg.

External survey in *case 16* at 7, 12 and 16 hours after infusion of Mg^{28} showed the greatest distribution of radioactivity over the liver and the next highest counting rate over the kidneys. Radioactivity over the bones was extremely low.

Other disease states (*case 19–25*). One patient with idiopathic epilepsy (*case 22*), one with renal tuberculosis (*case 24*) and one with hypertensive cardiovascular disease who was being actively treated (*case 25*) had serum magnesium levels below 1.30 mEq/l. The plasma clearance curves for Mg^{28}, specific activities of urine and plasma, and renal excretion of Mg^{28} and stable magnesium were all within the ranges found in normal subjects. Exchangeable magnesium values ranged between 2.9 and 5.4 mEq/kg; the highest value was found in a patient with acute lymphatic leukemia (*case 20*).

Serial specimens of washed erythrocytes were assayed for radioactivity content in four subjects (*cases 20, 23–25*). No radioactivity was detected in blood samples obtained up to 24 hours after the administration of Mg^{28}.

COMMENT

The low specific activity of the Mg^{28} currently available makes impossible true tracer studies of magnesium metabolism. Because of the low concentration, we were unable to follow plasma and urinary radioactivity with confidence beyond 36 hours. The doses of stable magnesium (12–30 mEq) usually administered intravenously, however, were considerably smaller than the loading dose of 97 mEq which produced a systemic reaction. For this reason, we feel that the data obtained in the present study may reflect the metabolism by the usual mechanisms of an extra load of magnesium rather than the chemical toxicity of this cation.

The results in normal subjects show that the stable magnesium infused with Mg^{28} was very rapidly cleared from the extracellular fluid. The intravenous administration of as much as 30 mEq of magnesium did not cause systemic reactions as long as the rate of infusion was slow enough so that the plasma concentration of magnesium did not exceed 3.0 mEq/l. The volume of fluid available for the dilution of this ion, as calculated from the plasma concentrations of Mg^{28}, exceeded the volume of total body water within a few hours. Since the amount of Mg^{28} excreted in the urine during this period was a small fraction of the injected dose, renal excretion alone could not account for this rapid clearance of Mg^{28} from the blood. The data obtained from tissue biopsies show concentrations of Mg^{28} in liver, appendix, fat, skin and subcutaneous connective tissue which cannot be attributed solely to the relative extracellular composition of these tissues. All of these observations suggest that Mg^{28} rapidly entered cells.

From previous studies (9, 10), in which large doses of magnesium were administered parenterally and deductions made from changes in the concentrations of stable magnesium in the blood or from the urinary excretion of this ion, it was concluded that magnesium was initially confined to the extracellular fluid and that excretion of the parenterally administered material was for the most part complete in 24 hours. A fraction of the

administered magnesium was thought to be bound to tissues. Our results suggest that, when 12–30 mEq of magnesium are infused slowly into normal subjects, 70% or more is retained in the body for at least 24 hours. The fact that the urinary excretion of stable magnesium during this time approximates the amount infused probably led previous investigators to the erroneous interpretation that most of the infused magnesium was rapidly excreted by the kidneys. Our data show that the infusion of a fairly large amount of magnesium results in a compensatory renal excretion of the body store of magnesium, and that the material excreted is not necessarily the ions which were administered.

After about 18 hours the specific activities in plasma and urine showed only a slight gradual decrease. These results suggest that the infused material had equilibrated in a rather labile body pool of magnesium, and that further exchange was occurring very slowly in a less labile pool. The size of the labile pool in normal subjects ranged between 135 and 397 mEq (2.6–5.3 mEq/kg of body weight). Previous analyses of entire adult human carcasses (11) have revealed the total body content of magnesium to be of the order of 1200–2400 mEq (27.2–35.1 mEq/kg of body weight). Thus, it appears that less than 16% of the total body content of magnesium is being measured by the present Mg^{28} exchange technique. These results contrast with those obtained in rabbits (6), in which species the values for exchangeable magnesium closely approximated the total carcass content of magnesium.

The results of the external survey and of the tissue analyses suggest that the labile pool of magnesium is contained primarily in connective tissue, skin and the soft tissues of the abdominal cavity (such as the liver and intestine), and that the magnesium in bone, muscle and red cells is exchanged very slowly. The fact that the Mg^{28} concentration was the same in samples of arterial and venous blood taken from the forearm is additional evidence for the slow exchange of magnesium in bone and muscle.

It is known that magnesium metabolism is related to that of phosphorus and glucose (12). Because the liver is so important in carbohydrate metabolism, and diabetes is so intimately related to carbohydrate metabolism, the results of the present study with Mg^{28} in patients with hepatic disease or diabetes mellitus are of particular interest.

A low serum magnesium concentration was found in the patient with the severest case of diabetes mellitus, who was acidotic at the time of the initial study. Mg^{28} was removed from plasma more rapidly than in any other subject studied and the cumulative renal excretion of Mg^{28} was rather low, although still within the normal range. The value for exchangeable magnesium in this patient (5.6 mEq/kg of body weight) was the highest found in this study. Similar results were obtained a week later, when the diabetes was under good control, except that plasma clearance was slower and the urinary excretion of stable magnesium was increased. The significance of these changes is not entirely clear. Studies in three other patients with diabetes gave results which did not differ from those obtained in normal subjects.

Mg^{28} studies in five patients with liver disease suggest that clinical evidence of magnesium deficiency does not occur until the liver has been severely damaged. The patient (*case 15*) who had the lowest initial serum concentration, together with a low value for exchangeable magnesium and high urinary excretion of Mg^{28}, died soon afterward in hepatic coma. It would seem that only a minimal amount of functional hepatic tissue is necessary to retain magnesium in the body. Another patient (*case 17*) had an exchangeable magnesium content of only 1.5 mEq/kg, but showed no clinical evidence of this abnormality.

Results obtained in patients with a variety of other diseases gave no definite clues concerning the factors regulating the metabolism of magnesium.

Our current knowledge concerning magnesium metabolism in human beings may be briefly summarized as follows: when magnesium is introduced into the body by the gastrointestinal route, the fraction absorbed is considerably smaller than had been suggested previousy (1). The factors regulating absorption across the gastrointestinal mucosa are not well understood, nor do we know how magnesium is transported from the portal system to the extracellular environment and eventually to the individual cells. It is not clear whether magnesium metabolism is dependent on a specific hormonal regulation. It appears to be related to the metabolism of phosphorus and glucose, and the liver seems to play a role. The labile pool of magnesium in the body, which is but a small fraction of the total body content of magnesium, is confined primarily to the soft tissues of the body. Magnesium exchange in bone, muscle and erythrocytes is extremely slow. Magnesium administered parenterally is excreted by the kidneys very slowly, but the over-all balance is maintained by a compensatory rapid excretion of endogenous magnesium.

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