STUDIES OF THE RENAL EXCRETION OF MAGNESIUM IN MAN * †

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Magnesium is one of the four principal cations in extracellular fluid, and in intracellular fluid is exceeded only by potassium; yet comparatively little is known about the mechanisms involved in the renal excretion of magnesium. That such is the case must be due to a variety of factors which include difficulties in chemical analysis, the binding by protein of a relatively large portion of the ion in serum, and the formation of soluble complexes which may be handled by the kidney in a different manner from that of the ion. Such difficulties probably account for the relatively few studies to date of magnesium excretion.

The experiments reported here involve 70 acute studies in man performed by usual clearance techniques. Renal hemodynamics and excretion rates of magnesium and other electrolytes were observed during multiple control periods and following eight principal experimental procedures. These were intravenous infusions of sodium lactate, sodium bicarbonate, acetazolamide, probenecid, sodium para-aminohippurate (PAH) to tubular saturation, magnesium salts, calcium salts and mercurial diuretics.

The data provide a basis for examination of factors likely to affect magnesium excretion and in some instances of probable renal mechanisms involved. The major part of filtered magnesium is reabsorbed by the tubules. The existence of a quantitatively small, but perhaps important, regulatory tubular secretion of magnesium is suggested by certain indirect evidence, but is not settled by present data. In addition to changes in filtered magnesium, consideration is given to possible effects on tubular magnesium transport of such factors as acid-base balance, possible relation to known active transport systems, specific interionic relationships especially with calcium or potassium, and formation of soluble magnesium complexes.

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† Portions of this work have been reported in preliminary abstracts (1–3).

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METHODS

General. Fifty-three normal men between the ages of 18 and 32 served as experimental subjects for one or more renal clearance studies by standard techniques (4) with bladder catheterization and standard water loading. Control results reported are averages from three or more periods of at least 15 minutes each which followed an equilibration period of at least 45 minutes.

Test procedures. The test procedure in each case consisted of the intravenous administration of some electrolyte solution or pharmacological agent. The eight major types of experiments are described below. Additional procedures were carried out to elucidate specific points and will be mentioned in appropriate sections. *1) Sodium lactate,* 2.4 mEq. per Kg. body weight, as a hypertonic (0.9 M) solution was given rapidly (10 minutes) in six studies. Whenever results of lactate administration are referred to without qualification in this report it should be understood that these are the studies meant. In four other studies alterations were made in the dosage or time of administration of lactate for comparison with the main series. *2) Sodium bicarbonate* was given to three subjects in dosage equivalent to the main lactate series. *3) Maximal rates of PAH transport* by the tubules (Tm_{PAH}) were achieved by standard techniques and observations at Tm_{PAH} were made in four studies for evaluation of the effect of PAH itself. In five additional studies after first attaining Tm_{PAH} the same hypertonic lactate infusion described previously was given to determine if the response was altered by prior PAH saturation. *4) Probenecid* (Benemid®) in total dosage of 3 Gm. was infused in seven subjects. Each study included three parts: control observations, measurements of the effect of probenecid alone, and then of the hypertonic lactate response after probenecid. *5) Acetazolamide* (Diamox®) was given intravenously in dosage of 5 mg. per Kg. body weight in 10 studies. *6) Mercurial diuretics* as 2 ml. of either meralluride (Mercuhydrin®) or mersalyl (Salyrgan®) were given in 15 studies. *7) Magnesium sulfate* was infused at rates not exceeding 1 Gm. per hour in five studies. *8)*

Calcium was infused over a 20 minute period as calcium chloride (0.7 Gm.) in five studies and as calcium gluconate (2 Gm.) in two studies.

Chemical determinations. Inulin, PAH, creatinine and phosphate were determined by methods previously indicated (5). Magnesium was determined by a titan yellow colorimetric method based on the methods of Heagy (6) and of Orange and Rhein (7). Following mercurial diuretics, aberrant results for urinary magnesium were found and subsequently shown to be due to an interference with the titan yellow method. If the mercury was first separated by means of H_2S precipitation, the method gave satisfactory results. The gluconate ion was also found to interfere with the titan yellow method. For this reason calcium chloride experiments were carried out in place of further calcium gluconate infusions and only these results are reported. Check of the magnesium by an independent phosphate precipitation method showed that changes in magnesium excretion, as well as those of the other ions, were very similar with either calcium salt. Calcium was determined by the Tisdall method as modified by Clark and Collip (8). Sodium and potassium were determined with a Baird internal standard flame photometer, chloride by the Volhard-Harvey modified method (9). Ultrafiltrate was obtained from the serum in a few studies by means of the capsule of Lavietes (10). In some studies the urine pH was determined on a Beckman pH meter. In most the pH was estimated to the nearest 0.1 unit by use of an appropriate short-range test paper. The latter method, while not suitable where precise knowledge of pH is necessary, was found to check well with a more accurate anaerobic method, the difference seldom exceeding ± 0.2 unit (11). Plasma pH was determined with a Beckman pH meter.

Statistical methods and graphical presentation. The excretion rates for each individual were expressed as a per cent of his control rate[1] and because of the large volume of data involved it was considered desirable to present only averages. For the purpose of testing statistical significance, nonparametric methods were used. These methods are somewhat less powerful (*i.e.,* less likely to demonstrate "significance") than the better known corresponding parametric "t" test. However, since fewer assumptions are necessary, significance that is demonstrated can be considered to have a more general application. The methods are considered more reliable for small samples and it is not necessary to make the assumption that the population distribution is normal in shape. Significance of changes from control rates was tested by the Wilcoxon matched-pairs signed-ranks test (13, 14). For testing significance where paired replicates were not available (*e.g.,* comparing results of two different test procedures) the Mann–Whitney U test was used (13). Confidence limits of 94 per cent were accepted rather than the 95 per cent convention for "significance" usual for parametric tests. The reason for this is that p values less than 0.06 cannot be obtained by the nonparametric methods used with five or fewer cases and that the results of these tests have somewhat greater generality than the parametric tests.

[1] A preliminary survey of the data showed a distinct tendency with most electrolytes under the conditions studied for the size of the change in different individuals to show a positive relation to the control rate as tested roughly by the quadrant sum test of Olmstead and Tukey (12).

RESULTS

The mean urinary excretion of magnesium during control periods for all studies was 6.3 μEq. per minute. Variability "between cases" (standard deviation of mean control values for individual studies) was ± 2.6 μEq. per minute; variability "within cases" (standard error of observation calculated as the standard deviation of individual measurements about the mean value for each individual) was ± 12.2 per cent of control.[2] The corresponding values for control plasma magnesium for the entire series were: mean, 1.83 mEq. per L.; S.D. ± 0.27 mEq. per L.; and S.E. of observation ± 3.6 per cent of control.

Effects of lactate administration

The results of the "main lactate series" are presented in Tables I and II and in Figure 1. The rate of magnesium excretion rose promptly to 227 per cent of the control rate during the infusion (*i.e.,* at time 8 minutes), reaching a peak of 261 per cent about 10 minutes later. It then fell back quite rapidly, reaching the control level within one and one-half hours. The excretion of other ions also increased, but somewhat less rapidly except for calcium and sodium (which was being infused). Also, in contrast to the response of magnesium, the excretion rates of sodium, potassium, chloride and phosphate all remained elevated. In absolute terms magnesium response was small relative to that of other ions but in terms of per cent of control the changes were comparable. Plasma magnesium changed only slightly and if anything decreased somewhat, perhaps secondary to urinary loss or to hemodilution. In any event,

[2] If a given experimental procedure were to cause neither any systematic change in the excretion of an electrolyte nor any change in variability from the control period, then there would be a 95 per cent chance that any randomly chosen single measurement would fall within the tolerance interval ± 2.2 S.E. of observation from that individual's mean control rate.

TABLE I

Effects of hypertonic sodium lactate, individual experiments*

Expt.	Time†	GFR‡	Urine flow	Urine pH	Urinary electrolyte excretion						Clearance§ Mg
					Mg	Ca	Na	K	PO_4	Cl	
	min.	*ml./min.*	*ml./min.*		*μEq./min.*	*μEq./min.*	*μEq./min.*	*μEq./min.*	*μMole/min.*	*μEq./min.*	*ml./min.*
1	−49										
	0	126	5.8	5.4	5.3	2.3	256	123	3.1	272	3.14
	+12	140	4.1		15.2	8.5	769	130	12.0	346	9.39
	+26	125	4.7	8.0	14.9	13.9	1,147	241	24.4	336	9.40
	+39	141	2.9	8.4	9.7	9.2	808	251	27.0	239	6.32
	+54	116	2.2	8.4	5.5	2.2	565	200	19.9	207	3.57
	+70	121	2.2	8.4	5.1	2.2	516	203	17.9	178	3.26
	+84	125	2.5	8.4	5.8	0.8	580	220	18.9	192	3.68
	+98	125	1.8	8.4	5.9	2.3	497	182	15.6	148	3.75
2	−52										
	0	119	9.8	6.0	6.8	0.9	241	119	26.2	284	4.04
	+17	124	11.5	7.4	18.1	20.6	1,234	183	31.7	375	11.10
	+31	114	5.7	7.8	11.9	12.9	1,065	246	34.8	366	7.55
	+48	112	2.8	8.0	8.7	6.1	648	288	30.2	250	5.33
	+64	125	2.2	8.4	9.1	5.0	556	288	28.5	204	5.61
	+80	114	1.5	8.4	7.6	3.8	421	246	21.2	134	4.51
	+94	111	1.1	8.6	6.4	2.3	328	228	15.3	108	3.50
	+110	102	1.2	8.6	6.0	2.4	301	205	13.9	88	3.59
3	−42										
	0	131	7.3	5.4	4.1		82	61	12.3	45.3	2.71
	+11	130	5.6		7.5		222	62	16.8	47.9	4.79
	+26	96	2.6	5.4	13.9		530	65	16.2	69.7	8.92
	+42	132	1.5	8.4	8.4		405	120	25.1	84.4	5.55
	+57	128	1.2	8.4	5.2		316	114	20.6	72.7	3.53
	+72	139	1.5	8.4	5.1		346	128	21.7	74.6	3.47
	+87	166	2.5	8.4	4.0		378	210	23.9	86.9	2.72
	+102	143	3.1	8.4	3.6		299	175	19.1	70.9	2.41
4	−44										
	0	123	9.3	5.4	2.6	1.5	99	61	13.1	65	1.49
	+12	130	11.7		5.3	14.9	509	72	11.4	104	2.97
	+28	106	3.6	8.2	9.3	17.2	657	122	25.6	116	5.22
	+42	127	2.3		5.8	10.3	522	157	25.2	116	3.39
	+58	141	3.0	8.4	4.8	8.7	537	180	24.2	142	2.82
	+72	132	3.0		3.7	6.3	465	155	19.9	126	2.20
	+86	136	3.6	8.4	4.1	6.2	522	151	18.3	135	2.41
	+100	118	4.3		3.0	3.9	428	154	13.4	116	1.77
5	−63										
	0	130	5.3	6.4	7.9	6.6	224	74	3.1	224	4.02
	+17	143	13.6	6.9	19.6	11.6	1,004	127	4.8	392	10.90
	+30	164	6.5	7.9	18.2	36.9	1,250	209	5.8	429	9.20
	+46	137	4.9	7.9	9.6	17.5	826	176	4.0	343	4.58
	+74	99	4.3	7.9	5.2	9.5	560	136	2.2	256	2.33
	+106	167	8.3	7.8	8.0	14.8	884	227	3.0	410	3.88
	+124	117	2.9	7.9	7.1		533	127	1.7	198	3.67
6	−47										
	0	90	8.5	5.4	17.9	20.3	226	99	18.8	168	7.45
	+13	104	2.2	5.4	24.8	32.4	417	101	14.2	179	11.30
	+26	112	5.3	8.2	31.1	53.7	1,045	247	28.2	272	16.00
	+40	99	3.2	8.4	23.1	34.4	768	240	29.4	251	11.80
	+56	96	3.9	8.4	21.0	29.9	842	211	24.7	333	11.00
	+73	104	4.4	8.4	20.0	30.2	908	211	20.8	344	10.70
	+87	101	4.0	8.4	18.2	27.2	850	200	28.5	292	9.60
	+109	96	1.9	8.4	16.9	25.7	743	181	19.8	249	8.74

* 2.4 mEq. per Kg. of body weight given intravenously in 10 minutes. Four additional studies with different dosage or time of administration of hypertonic sodium lactate are not included in the table.

† Data are expressed per individual periods which end at the time indicated, measured from the start of lactate infusion. The initial period is the average of three control periods.

‡ Glomerular filtration rate (inulin clearance).

§ UV/P, plasma magnesium uncorrected for binding to plasma proteins.

TABLE II

Summary of mean electrolyte excretion rates following various test procedures

Procedure, (No. studies) Electrolyte	Mean control	Excretion rate					
		+8 min.*	+20 min.	+36 min.	+50 min.	+65 min.	+80 min.
	μEq./min.	*Mean, % control*					
Sodium lactate (6)							
Mg	7.4	227†	261†	161†	124	112	109
Ca	6.3	745†	790†	437†	314	248	215
Na	188.0	384†	530†	391†	344†	328†	345†
K	89.7	129†	199†	226†	218†	210†	237†
PO_4	12.8¶	167	256	265	218†	197	204
Cl	176.5	137†	155†	143	142	133	138
Sodium bicarbonate (3)‡							
Mg	6.5	141	115	101	84	84	71
Ca	5.9	393	370	250	176	124	107
Na	196.9	439	460	335	341	295	181
K	74.0	241	332	284	264	250	228
PO_4	14.9¶	115	132	153	142	135	144
Cl	166.0	208	155	140	132	130	82
PAH-saturation (4)‡§							
Mg	6.8	136	161	178	187	159	166
Ca	7.0	214	322	367	390	346	323
Na	225.8	160	217	253	278	275	197
K	149.2	122	132	120	112	124	91
PO_4	16.4¶	157	202	171	156	152	151
Cl	271.2	91	86	85	84	86	92
Probenecid (7)§							
Mg	6.0	118†	108	108	121		
Ca	6.1	131	107	110	136†		
Na	149.7	167†	167†	175†	192†		
K	72.4	120	114	107	112		
PO_4	7.4¶	107	94	65†	56†		
Cl	160.3	148†	144†	148	158†		
Acetazolamide (10)							
Mg	6.9	102	87	84	92	96	98
Ca	10.9	194†	206†	211†	217†	228†	220†
Na	207.5	313†	400†	361†	345†	349†	320†
K	74.5	330†	471†	428†	387†	341†	307†
PO_4	13.0¶	157†	205†	224†	232†	204†	190†
Cl	208.9	192†	216†	212†	197†	162	144
Mercurials (15)‖							
Mg	4.8	190†	225†	263†	317†	402†	468†
Ca	6.2	226†	233†	328†	411†	536†	644†
Na	139.8	234†	323†	441†	564†	724†	880†
K	62.8	93	91	81†	77†	72†	74†
PO_4	16.4¶	132†	136†	127†	132†	125	121†
Cl	126.7	212†	281†	408†	498†	670†	873†
Calcium chloride (5)							
Mg	6.3	195	137	156†	176†	199†	190†
Ca	7.2	163†	211†	275†	348†	361†	345†
Na	123.7	146†	161†	167	168†	169†	152†
K	94.0	109	95	69	69	71	72
PO_4	12.9¶	100	93	78	80	78	63†
Cl	154.6	135	149†	153†	158†	168†	149†
Magnesium sulfate (4)‡							
Mg	13.5	169	189	327	428		
Ca	11.8	181	220	286	336		
Na	211.2	178	200	205	224		
K	162.8	76	77	72	75		
PO_4	19.8¶	160	210	209	205		
Cl	188.2	114	110	121	134		

* Measured from start of the test procedure.
† Significant change from control, Wilcoxon matched-pairs signed-ranks test.
‡ Not tested for significance because of small number of studies.
§ Effects of lactate after PAH-saturation or probenecid are not included (see Figure 4).
‖ Mersalyl (six studies) or meralluride (nine studies).
¶ Micromoles per minute.

the increased urinary excretion does not result from shift of magnesium into plasma, since any change in plasma magnesium concentration is in the other direction. No increase in proportion of ultrafiltrable magnesium was found in the two cases so studied. The increased urinary magnesium after lactate could not be attributed to changes in glomerular filtration rate, effective renal plasma flow or rate of urine flow. Changes in these factors were small and in opposite directions in individual cases, although the typical magnesium response occurred in all.

In two other studies a slightly smaller initial dose of lactate (100 mEq.) was given, followed by an additional 100 mEq. over the next hour. The rapid fall-off of magnesium excretion from the sharp peak reached soon after the initial lactate was not prevented by the continued lactate infusion, suggesting that stimuli for renal magnesium conservation may be promptly elicited and quite effective.

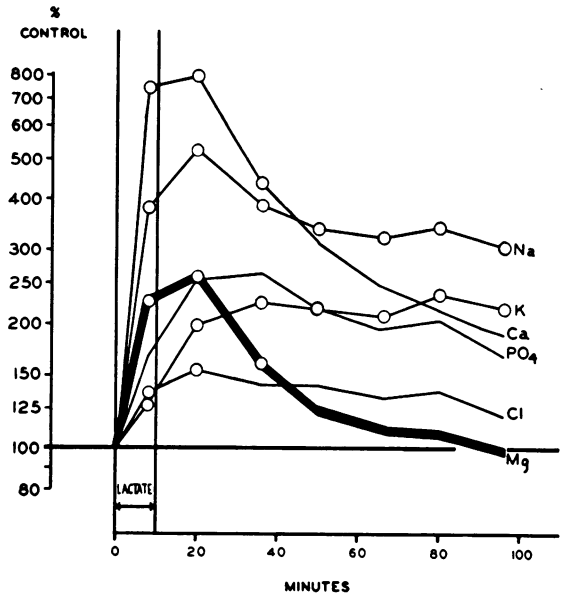

FIG. 1. RENAL EXCRETION OF ELECTROLYTES FOLLOWING INTRAVENOUS HYPERTONIC SODIUM LACTATE: MEAN CHANGES IN MAGNESIUM, SODIUM, POTASSIUM, CALCIUM, CHLORIDE AND PHOSPHATE

Each value is the mean from six experiments and is expressed as per cent of control rate. Changes from control that are statistically significant are represented by open circles.

Some comparisons with the lactate effect

Certain changes in excretion of the other major intracellular cation, potassium, are closely linked to acid-base changes. To examine the possibility of a similar relationship for magnesium the comparisons illustrated in Figure 2 were made. Three subjects were given equivalent doses of sodium bicarbonate in exactly the same manner as the usual lactate procedure. In per cent of control the average response after bicarbonate was 141 per cent at 8 minutes, 115 per cent at 20 minutes and had returned to control at 36 minutes. In none of the subjects was the peak UV_{Mg} response as large as even the smallest response in the lactate series, a significant difference between the series being demonstrated ($p = 0.02$, Mann–Whitney U test).

Figure 2 illustrates the comparative effects of lactate and bicarbonate, and also acetazolamide although other aspects of the latter will be considered separately. At the time of maximal magnesium effects, each type of procedure had produced a similar degree of alkalinity of the urine, yet the increases in magnesium excretion differed greatly in magnitude between bicarbonate and lactate and following acetazolamide there was actually a small decrease. Plasma pH similarly did not correlate well with magnesium excretion since bicarbonate had a somewhat greater effect on plasma pH than lactate in contrast to the effects on magnesium excretion. The excretion of potassium, on the other hand, appears in these data to be closely related to acid-base factors.

In two studies sodium acetate was given, the dose being reduced to one-half the usual lactate dose to avoid side reactions. A small increase in magnesium excretion (average 124 per cent of control at 8 minutes) was observed, similar in magnitude to that observed in two additional lactate studies with one-half the usual dose.

Tests of "inhibition" of the lactate response

An effect which is distinctly greater following sodium lactate than equivalent sodium bicarbonate brings to mind the relative effects of these substances on the tubular transport system handling para-aminohippurate (PAH), penicillin, phenol red and certain other substances (see Discussion). To examine a possible role of this transport system

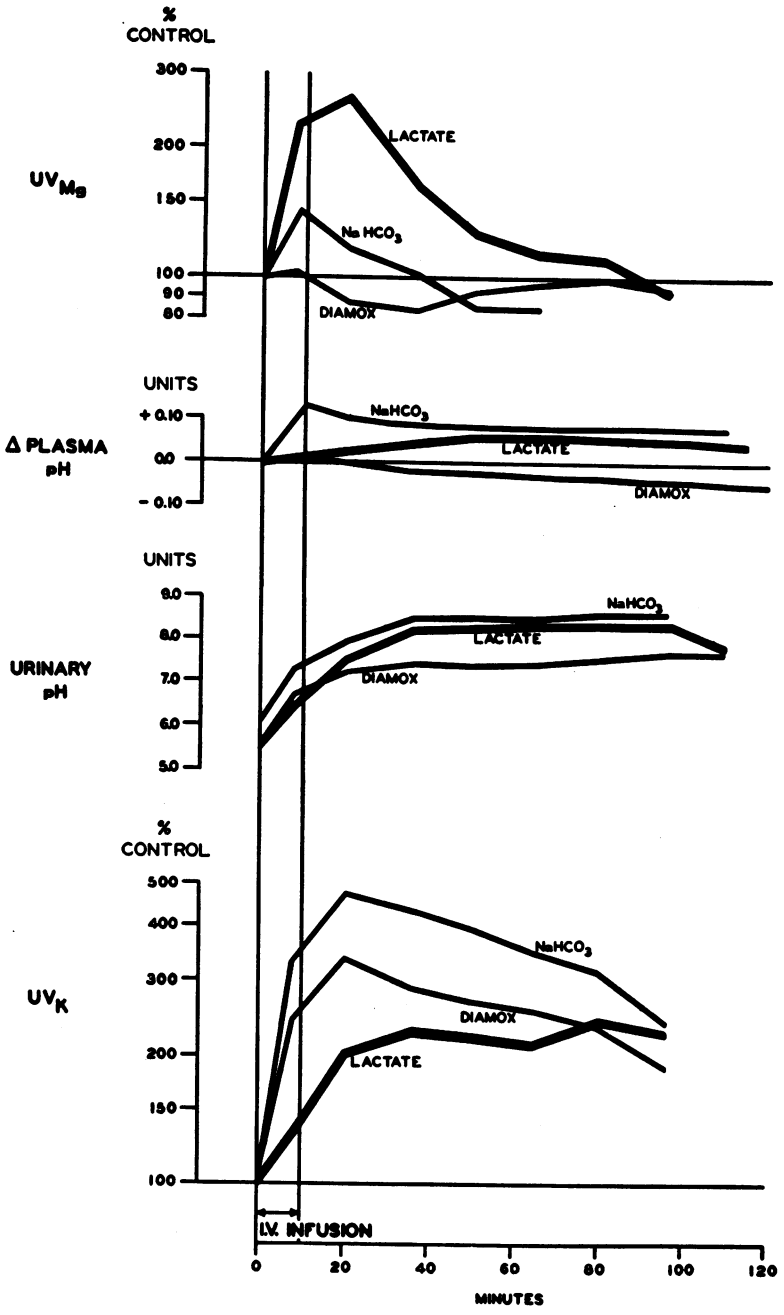

FIG. 2. COMPARATIVE EFFECTS OF LACTATE, BICARBONATE AND ACETAZOLAMIDE (DIAMOX®) ON MAGNESIUM EXCRETION, PLASMA pH, URINARY pH AND POTASSIUM EXCRETION

Mean values from six experiments with lactate, three with bicarbonate and ten with acetazolamide.

in magnesium excretion, the transport system was inhibited by probenecid or saturated by PAH administration. Results are illustrated by Figure 3. When lactate was given after either of these procedures the response in UV_{Mg} seemed to be reduced if expressed relative to the excretion after the "inhibiting" procedure. However, probenecid and PAH saturation without lactate administra-

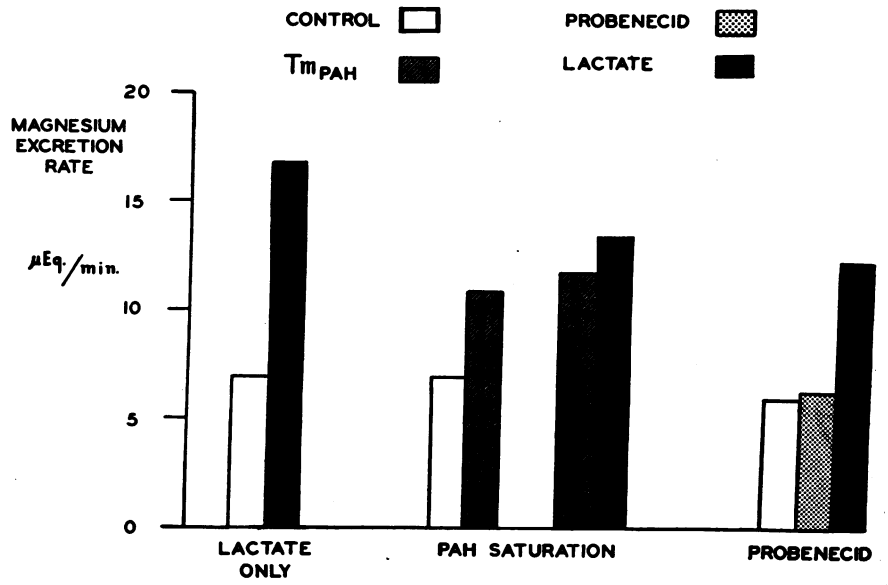

FIG. 3. EFFECTS OF PAH SATURATION AND OF PROBENECID ON MAGNESIUM EXCRETION AND ON URINARY MAGNESIUM RESPONSE TO HYPERTONIC LACTATE

Contiguous vertical bars represent mean values of consecutive parts of a single series of experiments. Lactate response is the mean at 20 minutes after start of the lactate infusion under each circumstance shown. See text for number of studies of each type.

tion appeared to cause increases in UV_{Mg} (Table II and Figure 3). The change following probenecid was extremely small, but consistent enough to reach statistical significance. When compared with the standard error of observation of 12 per cent of control it seems probable that the change after PAH saturation was also real, although the number of cases was insufficient to show "statistical significance." The average rate reached after lactate in μEq. per minute appeared somewhat smaller after both probenecid and PAH saturation than in the main lactate series. Nevertheless, expressed in these terms, in contrast to change from control, the differences between the various series were not statistically significant.

Effects of acetazolamide administration

Several features of the acetazolamide studies in addition to those mentioned above are illustrated by Figure 4 and Table II. At 20 minutes after infusion of the carbonic anhydrase inhibitor, UV_{Mg} averaged only 87 per cent of control and at 36 minutes, 83 per cent. Some decrease was observed in 9 out of 10 studies and, although small, was statistically significant for the series. This was the only one of the experimental procedures observed which caused a decrease of magnesium excretion below control levels. This decrease was closely correlated with a decrease in glomerular filtration rate, which averaged 86 and 85 per cent of control at 20 and 36 minutes, respectively.

Calcium excretion showed a distinct increase following acetazolamide. At the times of significant fall in the magnesium excretion (+ 20 and + 36 minutes) the calcium excretion rate averaged 206 and 211 per cent of control. Under other experimental conditions there was a noticeable similarity of behavior between UV_{Mg} and UV_{Ca} while comparisons of changes in excretion rates of magnesium with those for sodium, potassium, chloride and phosphate showed frequent examples of differences in time of maximum change and even sometimes in direction of change. Changes in UV_{Mg} were usually somewhat smaller both in μEq. per minute and in per cent of control than simultaneous changes in UC_{Ca}. Otherwise, the pattern of change was noticeably similar, except for the changes after acetazolamide when excretory rates of calcium as well as each of the other ions *except magnesium* showed a sharp increase.

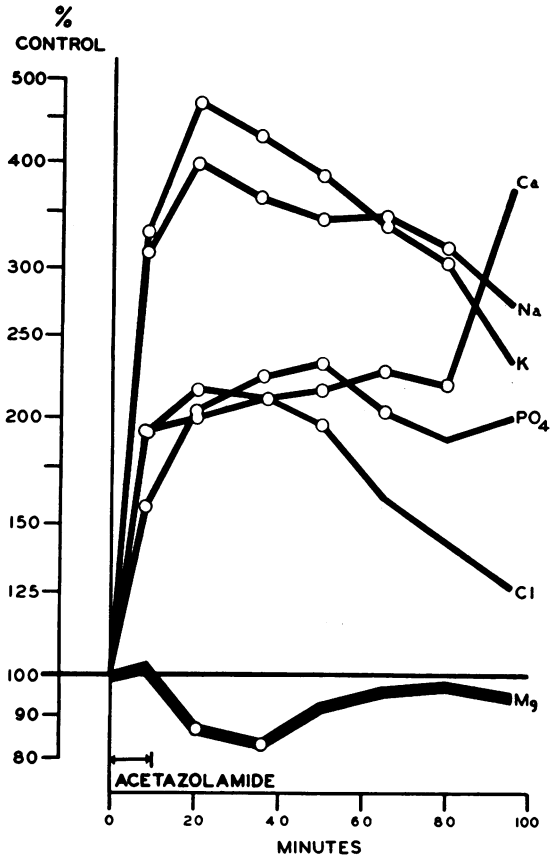

FIG. 4. RENAL EXCRETION OF ELECTROLYTES FOLLOWING INTRAVENOUS ACETAZOLAMIDE: MEAN CHANGES IN RENAL EXCRETION OF MAGNESIUM, POTASSIUM, CALCIUM, CHLORIDE AND PHOSPHATE

The data are presented as in Figure 1.

Effects of mercurial diuretics

Increased urinary excretion of magnesium was observed following injection of meralluride or mersalyl as shown in Table II. In contrast to the short peak observed following lactate, this effect was increasing throughout the period observed. The highest excretion rate observed (averaging 529 per cent of control) was at 96 minutes, which is beyond the times shown in Table II. On the average, potassium excretion decreased somewhat, a result clearly different from the distinct increase in UV_{Mg} and contributing one more situation where a definite difference was observed in the renal handling of the two major intracellular cations.

As measured by depression of the PAH transport system in the human kidney mersalyl is apparently about four times as potent as meralluride (15). In the present series the effects of these two mercurials on excretion of magnesium and other electrolytes were compared by studying six subjects once with each agent several weeks apart. There was little if any difference. Accordingly the results are reported together.

Effects of infusions of calcium and of magnesium

Changes in electrolyte excretion on administration of calcium chloride and of magnesium sulfate are presented in Table II. The administration of calcium chloride was followed by a marked increase in excretion of magnesium (as well as of calcium, sodium and chloride). A rather similar pattern was observed following administration of magnesium sulfate. Calcium excretion, like that of magnesium, sodium and chloride showed a definite increase. Changes in phosphate excretion were relatively small and variable following either magnesium or calcium administration. On the average potassium excretion decreased in both series. While this was small enough not to be statistically significant with the number of cases studied it is clearly different from the behavior of calcium and magnesium.

Ignoring the fact that part of the magnesium is bound or nonfiltrable, control excretion of magnesium was only about 3 per cent of that filtered. With the administration of magnesium it increased to only about 25 per cent of the amount filtered with the rather small infusions we were willing to give human subjects. Even with liberal allowance for protein binding it is obvious that no net tubular secretion of magnesium was demonstrated. In separate experiments on dogs we have been able to observe magnesium excretion of the same order of magnitude as magnesium filtration, making allowance for binding to plasma proteins (16). We have, however, not observed circumstances where excretion clearly exceeds simultaneous reabsorption to demonstrate a net secretion. A few observations did appear to suggest a small net secretion, but may represent experimental variation under these circumstances or the fact that the proportion of bound magnesium remains in some doubt.

DISCUSSION

The acute effects observed in the present studies are not always identical to reported changes in daily magnesium excretion after chronic administration of the same agents. The data, however, are particularly suitable for examination of renal mechanisms since they provide concurrent observations of a number of parameters at a time when physiological compensation is less likely to have obscured the primary events.

Changes in plasma magnesium and filtered load

Except when magnesium itself was infused, the experimental procedures reported caused only small changes in plasma magnesium and sometimes in different directions in different individuals. More often than not the average changes observed in these studies would cause filtered magnesium to change in the direction opposite to that in which UV_{Mg} changed.

The part of plasma magnesium bound to protein has been said to constitute anywhere from 14 to 52 per cent of the total, but most recent estimates under normal conditions (physiologic pH range, normal proteins) indicate that about 35 per cent of the total magnesium is protein bound (17–19). This ratio between ultrafiltrable magnesium and total serum magnesium probably remains relatively constant despite marked changes in total serum magnesium, a relationship previously observed for calcium (20). Changes in pH *within the ordinary physiological range* cause changes in proportion of calcium bound to protein so small as to be near or within the limits of accuracy of present experimental methods (21). From the similar way in which magnesium and calcium react with serum protein, this observation would probably also hold for magnesium. What data we have from ultrafiltration studies are consistent with these concepts. In any event it should be observed that any variations in proportion of filtrable plasma magnesium due to pH changes in our particular experiments would be expected to be in the wrong direction to account for the results observed.

In individual experiments changes in glomerular filtration rate appear to be the factor most likely to alter the rate of magnesium *filtration*. However, with most of the experimental procedures the filtration rate went up in some experiments and down in others; in either case the same type of change in urinary magnesium excretion was observed. Following acetazolamide, however, the filtration rate uniformly decreased and this change is a possible explanation of the observed decrease in excretion of magnesium.

Some observations on tubular magnesium reabsorption

The clearance of magnesium (calculated using the total plasma magnesium concentration) during control periods in 65 experiments averaged 4.0 ml. per minute with a range from 1.5 to 13.9 ml. per minute. It is evident that even if liberal allowance is made for protein binding of magnesium, the dominant (if not the only) renal tubular process is reabsorption. We have observed a number of conditions in which *decreased* tubular reabsorption is the most likely explanation of increased magnesium excretion. For example, mercurial diuretics, which are known to depress a number of tubular processes, caused a marked and sustained increase in the excretion of magnesium. None of the test procedures examined produced decreases in magnesium excretion except for acetazolamide, which also caused a fall in glomerular filtration rate. Such absence of demonstrated *increases* in reabsorbed magnesium is consistent with our previous suggestion (16), based on magnesium loading in dogs, that possibly tubular transport processes normally operate at or near saturation. The same observation, *i.e.*, that increments in filtered load of magnesium are excreted almost completely, has also been made by Chesley and Tepper on magnesium administration to pregnant and nonpregnant women (22). The conclusion that "basal" magnesium reabsorption is nearly maximal must be considered a tentative one, not only because of the indirect nature of the evidence, but because of the magnitude of possible experimental error.

Several groups are currently investigating the tubular site of magnesium transport in dogs by the stop-flow technique (23, 24) and a preliminary report indicates that ". . . magnesium is reabsorbed with greatest avidity in the distal part of the nephron at a site slightly proximal to that of maximal reabsorption of sodium and potassium" (24).

Is there a tubular secretory process for magnesium?

Hirschfelder suggested that most of the magnesium appearing in the urine is secreted by the tubules (25), an interpretation based on animal studies indicating that magnesium excretion is depressed by injury of the tubules more than by injury of the glomeruli and follows the excretion of phenolsulfonphthalein more nearly than that of xylose. He further pointed out observations of earlier workers that magnesium is excreted by the aglomerular kidneys of the toadfish. It has been indicated above that if a secretory tubular transport for magnesium exists at all in man or dog, it must be very small compared to concurrent reabsorption. Nevertheless, since it could play an important regulatory role, the question of its existence is not without importance. We have not, by magnesium loading in either men or dogs (16), encountered circumstances where "net" secretion was clearly present (i.e., where magnesium excretion clearly exceeded the rate of magnesium filtration). If changes in magnesium excretion were due principally to changes in tubular *secretion* one would anticipate that inhibition of this transport and therefore decrease of magnesium excretion below control levels would not be uncommon. Since none of our test procedures produced such decreases (except acetazolamide which also decreased filtered magnesium) regulation of tubular *reabsorption* as suggested above seems more likely. It has recently been demonstrated by radioactive magnesium injection during stop-flow analysis that nonfiltered magnesium can enter the distal nephron via the tubule (23). This may, however, represent only a back diffusion or flux in a direction opposite to the predominant movement of the ion. While a three-component system including tubular secretion is not excluded, present data may be explained by filtration and reabsorption alone.

Is magnesium excretion related to known tubular transport systems?

Lactate caused an increase in magnesium excretion which averaged approximately four times the increase observed after equivalent bicarbonate administration (Table II). Lactate also caused about four times the effect of bicarbonate on maximal tubular transport of PAH in man, both as reported earlier (26) and in a small series we have studied. Studies were therefore made of a number of other procedures known to influence the renal transport mechanism concerned with the secretion of PAH and certain other weak organic acids such as phenolsulfonphthalein, Diodrast® and penicillin. These included administration of probenecid, acetate, mercurial diuretics and PAH itself to Tm levels, and combinations of one of these procedures followed by lactate administration. Changes in magnesium excretion usually resulted, but there were enough differences between the patterns of Mg and of PAH response as mentioned above so that the nature of the relationship, if indeed there is any, is clearly not a direct one.

Another tubular secretory transport system has been recently suggested as involving synthesis and secretion of intermediates of the citric acid cycle (27). Malate secretion appears established and probably citrate and α-ketoglutarate are secreted under conditions of metabolic alkalosis (27). It is possible that magnesium might accompany such secreted organic acid, or that magnesium complexes formed after the anion reached the urine might interfere with magnesium reabsorption, but present data contribute no direct evidence to evaluation of such possibilities.

The role of soluble magnesium complexes

Magnesium, like calcium but in contrast to the univalent cations, has a marked tendency to form nonionized complexes, including chelate complexes. Only a small proportion of plasma magnesium is in the form of such soluble complexes, but magnesium excretion might be altered by any procedure that changes the concentration of complexing anions in the tubular lumen at the site of magnesium reabsorption. Present knowledge in this field is not adequate to assess the probable role of such processes. It would be necessary to know the concentrations of various potential complexing agents at the site involved, the pH at the required site, the tenacity of the bonds in the particular complexes and the relative manner in which the tubule handled magnesium ions, the complexing anions and the complex. Even if only the magnesium ion were reabsorbed the complex might not make the bound fraction unavailable for

reabsorption if immediate dissociation of complex occurred as fast as concentration of the free fraction was reduced. Similarly PAH is virtually completely cleared from plasma despite considerable protein binding.

Despite the manifest difficulty of quantifying the role of complex formation in magnesium excretion, there is some evidence suggesting that it may be important. After massive infusion of sulfate, which forms an incompletely dissociated salt with magnesium, Walser and Browder observed increased magnesium excretion in the dog from 6 to 70 per cent of filtered magnesium (28). Citrate warrants particular consideration, both because of its strong complexing property (29) and because it is responsible for the major part of the variation in urinary organic acid produced by metabolic acidosis and alkalosis (30). However, lactate infusion in dogs caused no larger change in citrate excretion than the small increase after bicarbonate (31), a result in contrast to the relative effects we observed on magnesium output. Such observations suggest that if complex formation is important in magnesium excretion it is often masked by other factors. Lactate is not likely to be of similar importance in this respect since the formation constant of the complex formed by magnesium with lactate is comparatively small (29).

Effect of acid-base changes

Although many procedures that affect acid-base balance also change magnesium excretion, our data demonstrate a clear separation between magnesium excretion and pH of either the urine or the plasma. The speculation that the pH within the tubular cells is more important might provide some improvement, but still not a good correlation with magnesium excretion. For example, comparative effects of lactate, bicarbonate and acetazolamide on UV_{Mg} (Figure 2) do not seem explicable by acid-base factors alone.

Are there specific interionic relationships, especially to potassium or calcium?

Our data do not indicate any consistent relations between excretion of magnesium and sodium, chloride, phosphate, or total ionic strength of urine.

Potassium excretion in man usually decreases following parenteral injection of magnesium salts (32, 33) (Table II). The hypothesis has been suggested that magnesium, a divalent ion, may enter into a univalent ion exchange mechanism, resulting in a decreased excretion of potassium (32). The failure of potassium chloride ingestion to produce a consistent effect on magnesium excretion does not lend support to such a suggestion (34). In contrast to the observations in man and to our own observations in dogs following infusion of magnesium sulfate, it has been reported that infusion of magnesium chloride in the dog markedly increased the excretion of potassium (24). In the present studies examination of the effects of various tests procedures (Table II) indicates that those procedures that produced the greatest changes in potassium excretion were associated with only modest changes in magnesium excretion and those procedures that produced the largest effect on magnesium excretion had comparatively little effect on potassium output, often causing a slight decrease.

Calcium and magnesium excretion showed a noticeable similarity of behavior with most of the test procedures (Table II). In Figure 1, for example, a similarity in shape of the curves for these two ions is evident. It is not clear whether this indicates some specific relation between magnesium and calcium or whether it results simply from the fact that a number of factors are likely to affect these chemically similar divalent ions in the same way. Magnesium infusion produced increased calcium excretion and calcium infusion produced increased magnesium excretion. Following acetazolamide, however, excretion of calcium increased markedly while magnesium excretion decreased somewhat. Apparently renal mechanisms regulating magnesium excretion are, at least partly, separate from those of other ions including calcium.

Effects of other factors

No consistent relationship was observed between excretion of magnesium and renal plasma flow (PAH clearance) or rate of urine flow. While changes in anion excretion may influence magnesium together with other cations in a nonspecific manner to maintain electroneutrality, such

effects are probably not predominant, as illustrated by the marked differences in response to lactate and to bicarbonate.

SUMMARY

By acute clearance techniques and various experimental procedures, in 70 studies in normal humans, factors influencing the renal excretion of magnesium were examined. Procedures included intravenous infusions of sodium lactate, sodium acetate, sodium bicarbonate, acetazolamide, probenecid, sodium para-aminohippurate (to tubular saturation), magnesium salts, calcium salts and mercurial diuretics alone and in certain combinations.

On infusion of hypertonic sodium lactate, excretion of magnesium increased to 261 per cent of control (average, six studies) within 20 minutes, then fell back rapidly, reaching the control rate within 90 minutes. Except for acetazolamide, each of the other procedures also produced an increase in magnesium excretion, although that following probenecid was quite small. The decrease following acetazolamide was coincidental with a fall in glomerular filtration rate and the increases in excretion after magnesium administration showed no definite differences from the probable increase in filtered magnesium.

Changes in glomerular filtration rate, urine flow, renal plasma flow, plasma magnesium and acid-base factors did not correlate well with magnesium excretion in most of the conditions tested. Many factors which affected the tubular transport system for para-aminohippurate also caused changes in magnesium excretion but there were enough differences to indicate that the relationship is not simple and direct.

It is suggested: *1*) that the major portion of filtered magnesium is reabsorbed by the tubules by processes operating normally at or near saturation; *2*) that such tubular reabsorption is the main regulatory process although tubular secretion cannot be excluded; and *3*) that renal mechanisms regulating magnesium excretion are, at least partly, separate from those of other ions including calcium and potassium.

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