EFFECT OF RENAL INSUFFICIENCY UPON PLASMA MAGNESIUM AND MAGNESIUM EXCRETION AFTER INGESTION OF MAGNESIUM SULFATE

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Although epsom salt has been used as a cathartic since its introduction by Grew in 1675, little has been known regarding the amount of magnesium actually absorbed from the bowel and excreted by the kidneys; and the effect of renal insufficiency upon this process has been entirely overlooked. We have found in the literature only two determinations of magnesium in the urine after ingestion of epsom salt. Hay (1) found 28.1 per cent of the magnesium excreted in 24 hours after one normal individual ingested 20 gm. of epsom salt (MgSO₄·7H₂O) and Yvon (2) found 21 per cent excreted after the same dose. In seven normal individuals we found, using the analytical methods described in the previous papers (3, 4), that 40 to 44 per cent (average 42.6 per cent) of the ingested Mg was excreted in the urine in 24 hours, while the plasma magnesium rose from an average concentration of 1.85 mg. of Mg per 100 cc. to an average concentration of 2.09 mg. (The greatest increase was 0.4 mg. of Mg per 100 cc.) In normal dogs and normal rabbits which received even larger doses (1 gm. of MgSO₄·7H₂O per kilo by stomach tube), the per cent of magnesium excreted and the rise of plasma magnesium were about the same. When doses of MgSO₄·7H₂O ranging from 2 gm. to 10 gm. per kilo were given by stomach tube to eleven normal rabbits, the per cent of magnesium excreted remained quite constant re-

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gardless of dose, ranging from 35.8 to 52.3 per cent (average 42.4 per cent). Four normal dogs excreted 42.6±3.7 per cent.

In six normal rabbits doses of 2.0 gm. of MgSO\textsubscript{4}·7H\textsubscript{2}O per kilo by stomach tube caused only a very small rise of plasma magnesium, from 2.03±0.14 mg. per 100 cc. to 3.01±1.27 mg. After doses of 4 gm. of MgSO\textsubscript{4}·7H\textsubscript{2}O per kilo in two rabbits, plasma magnesium rose in less than 4 hours to 4.04±0.89 mg. per 100 cc.; after 6 gm. per kilo in two rabbits it rose to 5.20±0.91 mg.; after 8.0 gm. per kilo in three rabbits it rose to 9.23±2.23 mg.; in three rabbits after 10 gm. per kilo it rose to 8.24±1.24 mg.; and in one rabbit after 12 gm. per kilo it rose to 11.99 mg. In four normal dogs the effects were similar but slightly greater than with 2 gm. of MgSO\textsubscript{4} per kilo, causing a rise of plasma Mg from 1.71 to 3.08 mg.; 3.0 gm., a rise to 4.7 mg.; 4.0 gm., a rise to 6.2 mg.; 6 gm., a rise from 2.4 to 10.7 mg.\textsuperscript{1}

None of these normal animals went into coma.

However, when MgSO\textsubscript{4} is given by mouth to nephrectomized animals or to animals whose kidneys have been injured by subcutaneous injection of HgCl\textsubscript{2} or cantharides, the result is totally different (Fig. 1). After double nephrectomy the plasma magnesium in four rabbits spontaneously rose gradually to reach a level of 16.8±0.8 mg. per 100 cc. after 5 days. They then just reached the concentration at which coma developed.

When magnesium sulfate was given by stomach tube to nephrectomized rabbits 24 hours after the nephrectomy the plasma magnesium rose rapidly (within 3 to 4 hours) to much higher levels than in the normal rabbits, and coma developed whenever the level of 17 mg. per 100 cc. was reached.\textsuperscript{2} The increases were as follows: In two rabbits after 2.0 gm. of MgSO\textsubscript{4}·7H\textsubscript{2}O per kilo by stomach tube there was a rise from 3.13±0.76 mg. to 10.11±1.16 mg.; in two rabbits after 2.5 gm. per kilo of MgSO\textsubscript{4}·7H\textsubscript{2}O, a rise from 3.38±0.49 mg. to 13.75 and 17.89 respectively (the second

\textsuperscript{1} Mg gluconate in doses equimolecular with 1 to 6.0 gm. of MgSO\textsubscript{4}·7H\textsubscript{2}O per kilo by stomach tube in normal rabbits or rabbits injected with HgCl\textsubscript{2} did not raise plasma Mg as much as did MgSO\textsubscript{4} (a maximum rise to 5.83 mg. of Mg per 100 cc. occurred in one rabbit injected with HgCl\textsubscript{2}).

\textsuperscript{2} This coincides exactly with the concentration at which Neuwirth and Wallace (5) found that coma occurred in normal animals after subcutaneous injection of MgSO\textsubscript{4}.
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animal was in coma); in three rabbits after 3.0 gm. per kilo, a rise from 3.08±0.63 mg. to 19.7±0.85 mg. (coma); in two rabbits after 4.0 gm. per kilo, a rise from 2.7±0.6 mg. to 17.83 and 27.8 mg. respectively (both in coma); in one rabbit after 6 gm. per kilo, a rise from 2.76 mg. to 32.0 mg. (coma); and in one rabbit after 8

\[ \text{Fig. 1. Effect of renal insufficiency on plasma and urine magnesium.} \]

\[ \text{Mg represents per cent of ingested magnesium excreted in urine in 24 hours;} \]
\[ \text{PSP, per cent of injected phenolsulfonphthalein excreted in the urine;} \]
\[ \text{X, per cent of xylose excreted in the urine. The white figures in black areas} \]
\[ \text{indicate gm. of MgSO}_4\cdot7\text{H}_2\text{O per kilo by stomach tube which cause corresponding increases of plasma magnesium (average figures).} \]
\[ \text{Coma occurs in all the animals whose plasma Mg is above 17 mg. per 100 cc.} \]

\[ \text{gm. per kilo, a rise from 2.17 mg. to 29.95 mg. (coma). Although} \]
\[ \text{in normal rabbits the Ca:Mg ratio is (3 - 4)/1, coma did not} \]
\[ \text{develop in the nephrectomized rabbits or other rabbits even when} \]
\[ \text{the Ca:Mg ratio fell to less than 1:1 unless the Mg was more than} \]
\[ \text{16 mg. per 100 cc.} \]
In six normal dogs after nephrectomy the plasma Mg gradually rose spontaneously during 4 to 6 days from a previous level of 2.43±0.7 mg. to from 9.47 to 20.9 mg. (average 15.4 mg.). Coma occurred in three dogs at 17 mg. of Mg or over. In nephrectomized dogs MgSO₄ by stomach tube produced much greater increases in plasma magnesium than in normal dogs. The increases were as follows: In one nephrectomized dog after 2.5 gm. of MgSO₄·7H₂O, per kilo, a rise from 2.15 mg. of Mg to 9.90 mg. in 3 hours; in three dogs after 3 gm. per kilo, a rise from 2.94±0.2 mg. to 18.24±0.5 mg. (all three in coma); in one dog after 4 gm. per kilo dose, a rise from 3.20 mg. to 20.7 mg. (coma); in one dog after 5.0 gm. per kilo, a rise from 3.0 mg. to 23.9 mg. (coma); in one dog after 6.0 gm. per kilo, a rise from 2.8 mg. to 26.87 mg. (coma); in one dog after 8.0 gm. per kilo, a rise from 3.47 mg. to 29.73 mg. (coma and rapid death).

In rabbits in which nephrosis with predominantly tubular injury was produced by subcutaneous injection of 5 to 15 mg. of HgCl₂ per kilo, the conditions were similar to but less marked than those following nephrectomy. In eight rabbits which received no MgSO₄ the plasma magnesium did not rise above 4.87±1.53 mg., to which level it rose gradually in 4 days. There was no evidence of coma. However, after the administration of MgSO₄ by stomach tube, much less magnesium was excreted by these nephrotic kidneys, in which the tubules were injured more severely than the glomeruli, and coma was induced easily. Corresponding to the pathological findings, the excretion of phenolsulfonphthalein was reduced from a normal of 86±5 per cent to 19.2±7; i.e., to 22.3 per cent of the normal. The xylose excretion was reduced to a much less degree, from a normal of 86.0±5.0 per cent to 66.1±5.0 per cent (76.8 per cent of the normal). In these rabbits with nephrosis due to injection of HgCl₂ the per cent of ingested magnesium excreted in the urine was 11.8±2.2 per cent (27.8 per cent of the normal). The ability to excrete magnesium and phenolsulfonphthalein are thus reduced to an almost equal degree, while the excretion of xylose is much less reduced.

After the administration of MgSO₄·7H₂O by stomach tube to rabbits which had previously been rendered nephrotic by 10 mg. of HgCl₂ per kilo, the following increases from previous levels of Mg per 100 cc. of plasma to maximum concentration reached 2 to
4 hours later were noted: in four rabbits after 2 gm. of MgSO\textsubscript{4}·7H\textsubscript{2}O per kilo (previous plasma Mg 2.16±0.23 mg.) a rise to 14±2.2 mg. (light coma or near coma) (two of these rabbits excreted 10.87±1.24 per cent of ingested Mg, i.e. 25.6 per cent of the normal excretion); in three rabbits after 2.5 to 2.75 gm. per kilo, a rise from 2.00±0.09 mg. to 16.26±5.0 mg. (coma); in three rabbits after 3.0 gm. per kilo, a rise from 2.34±1.08 mg. to 18.2±0.3 mg. (coma) (10.28±4.5 per cent of ingested Mg was excreted in the urine, i.e. 20.4 per cent of normal excretion); in three rabbits after 4.0 gm. per kilo, a rise from 2.07±0.11 mg. to 21.3±2.0 mg. (coma); in one rabbit after 5.0 gm. per kilo, a rise from 2.07 mg. to 28.7 mg. (coma); in one rabbit after 6.0 gm. per kilo, a rise from 2.2 mg. to 29.8 mg. (deep coma).

In rabbits which were given 1 cc. of tincture of cantharides (=0.6 mg. of cantharidin) per kilo subcutaneously, histological examination showed lesions of the glomeruli predominating over injury to the tubules. Corresponding to this, the phenolsulfonphthalein excretion fell to 23.4±5.9 per cent (27.2 per cent of normal), excretion of magnesium after ingestion fell only to 28.7±2.4 per cent (67.7 per cent of normal), and xylose excretion fell much more, to 16.1±2.4 per cent (18.7 per cent of normal). In four rabbits which received cantharides but no MgSO\textsubscript{4}, the plasma magnesium rose gradually during 3 days from a previous level of 2.05±0.05 mg. to 3.86±0.24 mg.

After the administration of MgSO\textsubscript{4}·7H\textsubscript{2}O by stomach tube to rabbits which had previously received 1 cc. per kilo of tincture of cantharides subcutaneously, the following increases in plasma were noted: In one rabbit after 2.0 gm. per kilo the plasma Mg rose to 5.9 mg.; in one rabbit after 2.5 gm. per kilo there was a rise from 2.27 mg. to 7.10 mg.; in three rabbits after 4.0 gm. per kilo, a rise from 2.35±0.05 mg. to 12.2±2.4 mg.; in one rabbit after 6.0 gm. per kilo, a rise from 1.86 mg. to 10.7 mg. None of these rabbits went into coma.

From these experiments it is evident that the plasma Mg rose less and the excretion of Mg in the urine was depressed less in animals injected with cantharides than in animals injected with HgCl\textsubscript{2}.

Since the excretion of magnesium in the urine runs more nearly parallel to the excretion of phenolsulfonphthalein than to the ex-
cretion of xylose, it seems probable that most of the magnesium is excreted through the tubules. This corresponds well to the observations of Smith (6), Marshall (7), and Bieter (8) who have shown that magnesium is excreted by the agglomerular kidneys of the toadfish.

In animals in which coma was induced by increased plasma magnesium from the ingestion of MgSO_4, the coma could be terminated instantly and complete return to consciousness and motility induced by the intravenous injection of CaCl_2. These animals lived longer than those which had not received CaCl_2 but not as long as those which had not received MgSO_4.

Administration of Na_2SO_4 in doses equimolecular with 1 to 12 gm. of MgSO_4 .7H_2O per kilo never brought on coma in normal animals or animals injected with HgCl_2. Sodium sulfate should therefore be the saline cathartic of choice in nephritic patients.

**SUMMARY AND CONCLUSIONS**

1. Normal animals and normal human beings excrete about 42 per cent of ingested magnesium in the urine in 24 hours. The per cent of magnesium excreted is fairly constant and is independent both of the dose and of the concentration of magnesium in the plasma.

2. Since the magnesium excretion is depressed by injury of the tubules more than by injury of the glomeruli and follows the phenolsulfonphthalein excretion curve but not the xylose excretion curve, most of the magnesium is excreted through the renal tubules.

3. In normal animals and normal human beings ordinary doses of ingested MgSO_4 scarcely raise the plasma magnesium.

4. In nephrectomized animals or in animals with injured kidneys, ingestion of MgSO_4 causes a rapid and intense increase in plasma magnesium, and may induce coma.

5. On account of this increase in plasma magnesium, it is probable that many clinical cases of coma in nephritic individuals, supposed to be uremic coma, are produced by the use of magnesium salts as purgatives. These patients could probably be resuscitated from this coma by the intravenous injection of calcium salts.

6. Sodium sulfate should be the saline of choice in patients with renal insufficiency.
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