Effect of vincristine, adriamycine and cyclophosphamide on selected indices of magnesium metabolism

Zusanna Araszkiewicz, Piotr Derentowicz, Michal Pirozynski and Adam Radomyski

Zusammenfassung

Es wurde der Einfluß der Zytostatika Vincristin, Adriamycin und Cyclophosphamid auf ausgewählte Parameter des Magnesium-Stoffwechsels an gesunden Ratten untersucht. Alle Zytostatika verursachten eine erhöhte Mg-Ausscheidung im Urin, die aber substanzabhängig war. Die ausgeprägtesten Steigerungsraten fanden sich mit +75,6 % nach Adriamycin, gefolgt von Cyclophosphamid mit +34,7 %, und Vincristin mit +33,9 %. Die Mg-Ausscheidung mit den Fäzes blieb unbeeinflußt. — Die Mg-Bilanz blieb stets positiv.

Summary

Effects of cytostatic agents on magnesium metabolism were studied by evaluating the effect of vincristine, adriamycine and cyclophosphamide selected parameters of magnesium metabolism in healthy rats. All agents have led to increased urinary magnesium excretion but this increase differed depending on studied agent. Administration of adriamycine produced the highest increase of urinary magnesium excretion by 75.6 %, cyclophosphamide increased it by 34.7 % and vincristine by 33.9 %. Faecal magnesium excretion remained unaffected. Magnesium balance was positive throughout the experiment.

Résumé

On a étudié l'influence des agents cytostatiques sur le métabolisme magnésique en évaluant les effets de la vincristine, de l'adriamycine et du cyclophosphamide sur des paramètres sélectionnés du métabolisme magnésique chez le rat en bonne santé. Tous ces composés ont entraîné une augmentation de l'excrétion urinaire de magnésium, dépendante de l'agent étudié. On a obtenu l'excrétion urinaire de magnésium la plus élevée après l'administration d'adriamycine (75,6 %), puis de cyclophosphamide (34,7 %) et enfin de vincristine (33,9 %). La concentration fécale de magnésium n'a pas varié. Le bilan magnésique est resté positif tout au long de l'étude.

Introduction

Wide use of cytostatics in medicine enhances finding their various new side effects. During the last few years hypomagnesaemia observed during cis-platin therapy attracted much attention [4, 12, 16, 18, 19, 23]. Due to the fact that cis-platin is usually used in combination chemotherapy with other agents, one may doubt if this agent alone produces hypomagnesaemia or, maybe, other cytostatic agents contribute to it. This may be so as adriamycine, one of the most often used agents has a very similar chemical structure to that of aminoglycosides, which are known to produce hypomagnesaemia [10, 17, 18]. Decreased serum magnesium levels are also seen following antibiotics used in immunosuppressive therapy (cyclosporine) [20] and following administration of antifungal agents (amphoterracine B) [3]. The neoplastic process by itself may also produce disorders of magnesium metabolism [6, 7, 13, 14].

Bearing in mind the importance of magnesium and its role in the living organism [22] we wanted to find out if other widely used cytostatic agents, excluding cisplatin, such as vincristine, adriamycine, cyclophosphamide affect magnesium metabolism. The study was carried out on healthy rats, evaluating the effect of each drug on magnesium metabolism using the balance method.

Department of Internal Medicine and Department of Immunology Institute of Tuberculosis, Warszawa/Poland

Materials and methods

Inbred male Wistar rats of a mean body weight 243 ± 8.09 g from the Oncology Institute (WAG/G) were used. Animals were isolated in metabolic cages. All received a controlled amount of feed that contained 6.77 mmol of magnesium in 100 mg and an unlimited volume of water. Twenty six rats were divided into three groups. All cytostatic agents were administered intraperitoneally in a single dose exceeding fivefold the one used in combination chemotherapy in humans.

Group I (8 rats) received Vincristine (Richter) in a dose 0.15 mg per kg b. w. Group II (9 rats) received Adriamycine (Farmitalia) in a dose 5 mg per kg b. w.; Group III (9 rats) Cyclophosphamide (Germed) in a dose 50 mg per kg b. w. was administered.

Each experiment lasted four weeks. It was always preceded by a four day adaptation period followed by a week long control after which the cytostatic agent was administered. During the control period and the following 3 weeks magnesium levels were determined in daily urine and faeces samples. Urine magnesium excretion was determined in four

daily samples, after which the results were added. Faecal magnesium was determined in four day pooled samples. The four day urinary and faecal excretion of magnesium was assumed to be representative of weekly excretion of magnesium.

Once a week daily urinary excretion of hydroxyproline was determined. Magnesium in urine and faeces was determined by mass spectrophotometry (Electrolytautomat — Opton). Faeces were examined following carbonization in a silicone chamber in the temperature of 900 – 1000 °C for 24 hours. Urinary hydroxyproline was determined using the Stegemann method.

Statistical analysis was performed using Student's test for paired values at a level of $p = 0.05$.

Results

Data concerning urinary magnesium and hydroxyproline excretion, dietary intake and faecal excretion of magnesium, and balances of magnesium are summarized in Fig. 1.

Group I (vincristine)

Increased 24 hour urinary magnesium excretion ($p < 0.05$) was observed during the first week after vincristine administration. During the second week increased urinary excretion of hydroxyproline was observed ($p < 0.01$).

Dietary intake of magnesium decreased during the first week ($p < 0.001$) and increased during the second and third week ($p < 0.05$, $p < 0.01$ respectively).

Decreased faecal magnesium was observed during the period of decreased dietary intake ($p < 0.001$). In the remaining weeks it did not differ from control values.

Magnesium balance remained positive through out the experiment and increased during the second and third week ($p < 0.001$, $p < 0.001$ respectively).

Group II (adriamycine)

Significantly increased 24 hour urinary excretion of magnesium was observed during the first and second week ($p < 0.001$). At the same time decreased excretion of hydroxyproline was observed ($p < 0.05$, $p < 0.01$ respectively). Dietary intake of magnesium decreased during the first week ($p < 0.001$) and increased during the next two weeks ($p < 0.05$, $p < 0.001$ respectively).

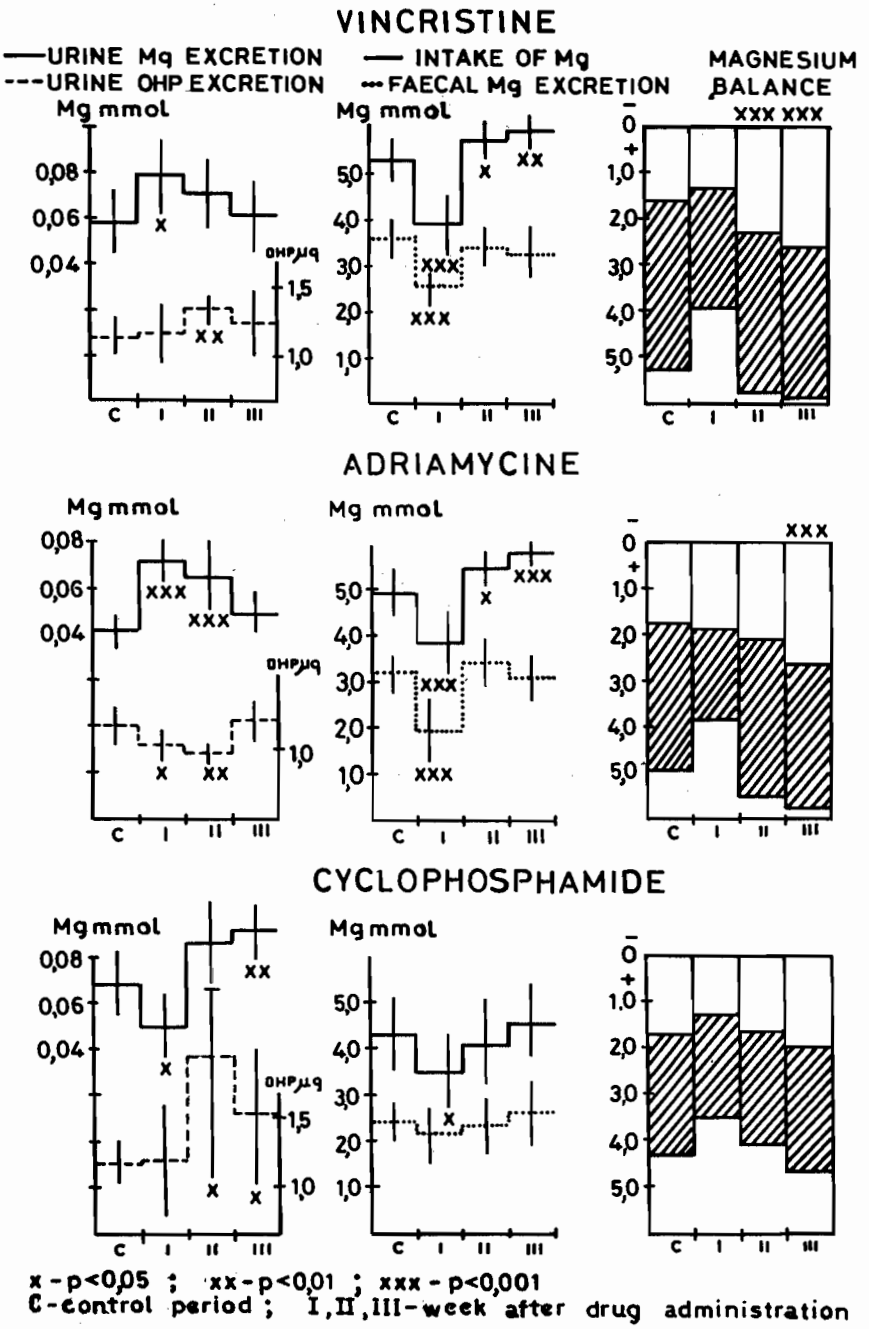

Fig. 1: Excretion of magnesium and hydroxyproline in urine; intake and excretion of magnesium in faeces; magnesium balance before and after administration of drug (Mg = magnesium, OHP = hydroxyproline)

Decreased faecal magnesium excretion was observed during the period of decreased dietary intake of magnesium ($p < 0.001$) and during the subsequent two weeks did not differ from control values.
Positive magnesium balance was observed throughout the experiment, being statistically significant during the third week ($p < 0.001$).

Group III (cyclophosphamide)

Increased 24 hour urinary excretion of magnesium was observed in the third week of the experiment ($p < 0.05$). Increased levels of urinary hydroxyproline were seen during the second and third week ($p < 0.05$).
Dietary intake of magnesium decreased during the first week ($p < 0.05$) and did not differ from control values during the subsequent two weeks.
Magnesium balance remained positive throughout the experiment.

Discussion

We chose an experimental model with healthy animals to study effects of cytostatic agents on magnesium metabolism. This enabled us to evaluate each agent separately and eliminated the possibility of the neoplastic derived disorders to influence the results [6, 7, 13, 14]. Three cytostatic agents selected for this study are presently the most commonly used in treating malignant diseases. Each one has different action mechanisms — vincristine is an alkaloid, adriamycine an antibiotic and cyclophosphamide an alkilating agent.
The used balance method enables to evaluate excretion of magnesium in urine, faeces and dietary intake of magnesium. The ratio of magnesium content in diet and faeces provides a rough estimate of magnesium absorption in the digestive tract. Determination of urinary hydroxyproline excretion is an accepted method of studying bone collagen metabolism [2]. Increased urinary hydroxyproline levels indicate increased degradation of bone collagen and possibly concurrent mobilization of magnesium ions bound to it [2]. The observed phenomenon are interesting because one must remember that a half of the body's magnesium is stored in bones [9]. The kidney is the main regulating organ of magnesium metabolism. 50 to 70 percent of the filtered magnesium ions are reabsorbed in the ascending limb of *Henle's* loop, 15 to 30 percent in the proximal tubule and 2 to 5 in the distal tubule [15]. These mechanisms enable modulation of magnesium urinary excretion. The mechanism of magnesium reabsorption is controversal, presumably to be partly of passive nature [15]. Parathormone increases reabsorption of magnesium, its action being mediated by cAMP, in the ascending limb of Henle's loop [8].
All three cytostatic agents used in this study increased magnesium urinary excretion, although not to the same degree, and the mechanism leading to this effect also seems to be different. Following administration of vincristine rats excreted 33.9 % more magnesium compared with control values. Adriamycine increased magnesium urinary excretion by 75.6 %, and cyclophosphamide by 34.7 %. Determination of urine hydroxyproline level is of help in considering pathomechanisms of the above mentioned phenomenon. Rats that received vincristine also excreted higher amounts of hydroxyproline in the urine, which may account for destruction of bone matrix collagen.
Increased urinary excretion of magnesium and hydroxyproline may be interpreted as a sign of osteolysis. One may assume that the excreted magnesium was derived from the bone pool. Increased dietary intake of magnesium did not influence urinary excretion of this ion because it was observed later than the increase of magnesium excretion.
A different mechanism of magnesium loss could be proposed in animals that received adriamycine. Low hydroxyproline levels in daily samples of urine imply that the observed hypermagnesuria was not due to osteolysis. Low parathormone levels were demonstrated in a woman treated with cis-platin [12] and patients treated with adriamycine and citarabine [11]. Although the combined chemotherapy used in these cases does not help in formulating conclusions, but since one of the used agents was adriamycine, also tested by us, it is possible that similar mechanisms were present in our experimental model.
Decreased serum parathormone levels indicate some degree of decreased parathyroid function which results in decreased physiological bone reconstruction, causing decreased urinary hydroxyproline excretion. The decrease in hydroxyproline urinary excretion, observed in our study, indirectly may imply that adriamycine affected the function of the parathyroid glands, by decreasing it. Parathormone increases reabsorption of magnesium in renal tubules [1]. Low parathormone levels decrease reabsorption of magnesium resulting in increased magnesium excretion. Thus it seems justified to propose that increased magnesuria in this experiment was caused by decreased parathormone action. Furthermore adriamycine being a well known nephrotoxic agent [5] may also produce increased urinary excre-

tion of magnesium due to damage of renal tubules. In this experiment we cannot exclude the effect of increased magnesium dietary intake on increased magnesium urinary excretion.

Cyclophosphamide produced and augmented prolonged urinary excretion of hydroxyproline suggesting some form of collagen metabolism disturbance. Possibly increased magnesium excretion was due to mobilization of this ion from the bone pool.

None of the studied agents increased faecal excretion of magnesium. After a decreased dietary intake of magnesium, immediately following administration of the cytostatic agent, later on dietary intake of magnesium was increased. Positive magnesium balance values, observed in all experiments, was more pronounced following administration of vincristine and adriamycine.

This study demonstrated that magnesium is solely excreted by the kidneys. Probably the studied cytostatic agents only transiently affected the kidney saving mechanisms of the magnesium ion. This could lead to increased intestinal absorption of magnesium. This hypothesis is supported by the fact that excretion of magnesium in faeces remained unchanged despite increased dietary intake.

Disturbances of magnesium metabolism following administration of cis-platin although seemingly similar were quite different. Increased urinary magnesium excretion was also observed in patients receiving cis-platin for prolonged time [12, 16, 19, 22]. The increased magnesium urinary excretion in these patients was accompanied by increased loss of magnesium from the alimentary tract (emesis, diarrhea). One must also bear in mind that malignancy produces taste disturbances that have been incrimitated and linked to observed anorexia in such patients, leading to decreased dietary intake of magnesium. Prolonged hypermagnesuria could not be corrected by increased dietary intake, as it was seen in our study. It seems that inability of correcting renal loss of magnesium by increasing absorption in the alimentary tract leads to a clinical picture of hypomagnesaemia during cytostatic therapy.

Data from this study demonstrate that disturbances of magnesium metabolism during chemotherapy may be induced not only by cis-platin, but also may be seen during therapy with other agents, such as vincristine, adriamycine and cyclophosphamide.

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(For the autors: Dr. *Zusanna Araszkiewicz*, Institute of Tuberculosis and Lung Diseases, Plocka 26, PL-01-138 Warszawa/Poland)