Clinical and experimental aspects of cisplatin-induced hypomagnesemia

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ABSTRACT

This PhD dissertation is the result of the work carried out between 2000 and 2003 at the Departments of Oncology, Cardiology and Anaesthesiology, Rigshospitalet, Copenhagen and the Department of Pharmacology, The Panum Institute, Copenhagen. The thesis is based upon one review article, a prospective clinical study and two experimental studies.

Hypomagnesemia affects more than fifty percent of patients receiving cisplatin-containing chemotherapy. Despite that many resources have to be allocated to prevent or correct this complication very little is actually known about the clinical importance of cisplatin-induced hypomagnesemia. Accordingly the therapeutical approach to hypomagnesemia remains controversial. Magnesium is almost entirely located in the intracellular compartment in the body.

The clinical study evaluated skeletal muscle magnesium (Mg) and potassium (K) during treatment with cisplatin and the predictive value of plasma (P)-Mg for intracellular Mg during cisplatin treatment. Following treatment with a total dose of ≈500 mg (270 mg/m^2 surface area) cisplatin over 80 days (3 cycles) a ≈15% decline in P-Mg was accompanied by a ≈15% loss of muscle-[Mg] as well as a ≈10% reduction of muscle-[K] and fatigue and muscle weakness previously ascribed to hypomagnesemia may therefore also be well explained by muscle K depletion observed despite normal levels of P-K. There was no correlation between P-Mg and skeletal muscle-Mg or between P-K and skeletal muscle-K. Thus, P-Mg and P-K are not reliable indicators for Mg and K depletion during treatment with cisplatin. However, the majority of patients will present Mg and K depletion after cisplatin therapy, and of these only very few patients will present a P-Mg or P-K outside normal reference values. Therefore, routine supplementation should be considered in all patients receiving cisplatin.

The first experimental study investigated the role of Mg on cisplatin-induced changes in renal function. The study indicated a substantial additive effect of Mg depletion on cisplatin-induced renal toxicity as evidenced by significant changes in plasma creatinine and urea, renal failure induced mortality and loss of renal transporters: Na,K-ATPase (α-subunit), the Na,K,2Cl-cotransporter NKCC2, the type III Na,H-exchanger NHE3, aquaporins 1 (AQP1) and 2 (AQP2). This should give cause for concern since the nephrotoxicity observed during cisplatin treatment might be substantiated by the known Mg loss associated with cisplatin treatment especially in patients suffering from intense gastro-intestinal side effects.

The purpose of the second experimental study was to investigate changes in renal and intestinal homeostasis of magnesium and potassium during cisplatin treatment in rats to provide guidelines for human supplementation studies. The study demonstrated that the Mg loss associated with cisplatin treatment is mainly the result of lowered intestinal absorption and not as presently thought the result of increased renal wasting. Instead an increased renal reabsorption capacity was observed in response to decreased intestinal absorption. It further showed that Mg and K metabolism are subject to predictable changes in intestinal absorption and renal excretion with each cisplatin treatment, and that knowledge of these changes might be used in planning supplementation. Thus, the experimental observations support intravenous supplementation one and two to three days after treatment followed by oral supplementation until the next treatment.