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A Randomised Study to Determine Whether Routine Intravenous Magnesium Supplements are Necessary in Patients Receiving Cisplatin Chemotherapy with Continuous Infusion 5-Fluorouracil

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Cisplatin is an effective antineoplastic agent, but can cause renal tubular damage leading to urinary magnesium wasting and hypomagnesaemia. Cisplatin and 5-fluorouracil, when used in combination, have synergistic antitumour activity in upper gastrointestinal malignancies, but it is unclear whether they have additive effects on renal magnesium loss. To determine the optimal regimen for magnesium supplementation in these patients, we have conducted a randomised trial of routine intravenous magnesium supplements compared with magnesium given on an 'as required' basis. 32 patients were randomised to receive magnesium intravenously in prehydration and posthydration fluids with cisplatin chemotherapy, or to receive magnesium only when the serum level was low. 5-fluorouracil was given as a continuous infusion. Serum magnesium was measured on admission for each cycle of chemotherapy and an interim measurement performed between each cycle. 28 patients were evaluable. All patients randomised to receive magnesium on an 'as required' basis had at least one episode of hypomagnesaemia. On subsequent admissions for chemotherapy (cycles 2 and 3), the mean serum magnesium level was significantly lower in these patients compared with patients who received magnesium routinely ($P < 0.05$). After omission of magnesium from the first cycle of cisplatin, magnesium supplements were necessary in 50% of subsequent cycles, usually by the second or third cycle. Moreover, there were several instances of symptomatic hypomagnesaemia requiring further intravenous supplements in mid-cycle. Patients treated with a combination of cisplatin and 5-fluorouracil should be given intravenous magnesium supplements with each cycle of cisplatin chemotherapy. Nevertheless, episodes of hypomagnesaemia still occur, and additional intravenous supplements may be required, highlighting the importance of measuring this electrolyte.

Key words: magnesium, cisplatin, 5-fluorouracil
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INTRODUCTION

CISPLATIN is an effective antineoplastic agent when used either alone or in combination in the treatment of many tumours, including gastrointestinal malignancies. However, major electrolyte abnormalities are a well-recognised toxicity of cisplatin therapy [1–4]. Hypomagnesaemia and renal wasting of magnesium in association with cisplatin therapy was initially described in 21 of 37 evaluable patients by Schilsky and Anderson in 1979 [5], and this has been repeatedly confirmed [6–9]. The kidney is the major regulator of the circulating magnesium concentration, and renal tubular magnesium wasting is thought to be the mechanism of cisplatin-induced hypomagnesaemia [10]. There also appears to be a dose-toxicity relationship [7]. The majority of patients with hypomagnesaemia have no symptoms or signs, but its manifestations can include weakness, confusion, neuromuscular irritability, seizures, and ventricular arrhythmias [11–14], and can cause considerable morbidity. These effects can sometimes be difficult to differentiate from the toxicity of chemotherapeutic agents or from the cancer itself.

It has been suggested by some authors that routine magnesium supplements become part of cisplatin-containing regimens [13, 15], whilst others have suggested that this does not prevent occurrence of hypomagnesaemia [2, 3] and have questioned the value of giving it routinely [4].

In a recent randomised study continuous administration of oral magnesium supplements was considered to be superior to intermittent administration because virtually all patients randomised to the latter arm eventually required oral magnesium supplements [16]. Patients requiring magnesium supplements on an 'as required' basis only did so following two courses

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of chemotherapy, and no patient developed systemic effects consistent with hypomagnesaemia. Nevertheless, administration of oral supplements may lead to gastrointestinal disturbance, and have been reported by some patients to be unpleasant to take, with subsequent non-compliance [13]. One group has suggested that the effect of cisplatin on renal wasting of magnesium is cumulative, with no actual depletion of magnesium from body stores until the third course of cisplatin therapy [17]. However, a prospective study of serum magnesium in 50 patients has shown that all patients will become biochemically hypomagnesaemic within 3 months of starting therapy, with 10% experiencing symptoms and requiring magnesium supplements [18].

There is evidence that cisplatin and 5-fluorouracil (5-FU) have synergistic antineoplastic activity [19, 20]. Higher response rates have been achieved when 5-FU is given by low dose continuous infusion rather than by intermittent bolus injections. We are therefore using this combination together with epirubicin (ECF) in the management of gastric and other upper gastrointestinal malignancies [21]. It is not clear if the addition of 5-FU by continuous infusion has any additive effect on the cisplatin-induced renal magnesium wasting in this group of patients. Previous reports of the use of this regimen in Phase II trials in the management of gastric cancer [22] and breast cancer [23] do not comment on the effect of this regimen on serum magnesium.

To determine the optimal regimen for magnesium supplementation, both in terms of patient morbidity and cost-effectiveness, we performed a randomised trial, comparing routine administration of intravenous (i.v.) magnesium supplements, with i.v. magnesium supplements given on an 'as required' basis, in patients treated with a combination of cisplatin and 5-fluorouracil.

PATIENTS AND METHODS

Patients

32, consecutive, previously untreated patients with upper gastrointestinal tumours, receiving ECF chemotherapy, were randomised into this study. All patients received 5-FU 200 mg/m^2/day by continuous infusion through a Hickman Line, with cisplatin (60 mg/m^2) and epirubicin (50 mg/m^2) given every 21 days. All patients received standard antiemetic and hydration protocols with the cisplatin therapy.

Glomerular filtration rate (GFR) was measured prior to starting chemotherapy, and also routinely before the fourth cycle of ECF. In addition, GFR was measured before other cycles if indicated, e.g. if initial GFR < 60 ml/min, or in the presence of deteriorating renal function as indicated by blood urea and creatinine measurements. Patients with a GFR of > 60 ml/min received the full dose (60 mg/m^2) of cisplatin; if the GFR was < 60 ml/min, then the dose of cisplatin was reduced, such that the dose of cisplatin given in milligrams was equal to the GFR. If the GFR was < 40 ml/min, no further cisplatin was given. Serum magnesium was measured in all patients on admission for chemotherapy, together with an interim measurement between each cycle of treatment, and on other occasions, if clinically indicated.

Patients randomised to receive magnesium were given a total of 12 mmols of magnesium intravenously with prehydration fluids, and a total of 16 mmols of magnesium in the posthydration fluids, according to our standard practice. Patients randomised to receive magnesium on an 'as required' basis only received it if the previous interim magnesium level was low (< 0.7 mmol/l), and/or if the serum magnesium level on admission for chemotherapy was low (< 0.7 mmol/l). Patients with markedly low interim serum levels (< 0.6 mmol/l), or with low interim serum magnesium levels and symptoms suggestive of hypomagnesaemia were admitted for intravenous magnesium infusion in mid-cycle. Patients with persistent hypomagnesaemia, despite intravenous supplements, were started on oral supplements (magnesium glycerophosphate tablets thrice daily). Symptoms of hypomagnesaemia were evaluated on admission for each cycle of chemotherapy.

Statistical Methods

All patients who completed two or more cycles of chemotherapy were considered evaluable. Patients were not randomised to receive magnesium routinely or on an 'as required' basis at each cycle of chemotherapy, as the effect of cisplatin on renal magnesium wasting is thought to be cumulative. The Mann-Whitney non-parametric test was used to compare the serum magnesium levels between the two groups.

RESULTS

28 of the 32 patients randomised into this study were evaluable. 3 of the 4 non-evaluable patients died after the first cycle of ECF, and the fourth patient was excluded because of a protocol violation. There were 14 evaluable patients in each arm of the study. There was no significant difference in the mean age, mean baseline GFR and the mean baseline serum magnesium level between the two groups (Table 1).

Of the 14 patients randomised to receive magnesium supplements, 7 (50%) patients completed all six cycles of ECF and 7 received four or fewer cycles. A total of 64 cycles were given (median = 5 cycles). 1 patient did not receive epirubicin with his second (final) course of ECF because of a markedly abnormal liver function. In the 'as required' magnesium group, 9 (64%) patients received all six cycles of ECF, and 5 received four or fewer cycles. A total of 71 cycles (median = 5 cycles) of chemotherapy were given. 2 patients (who received three and six cycles, respectively) received no epirubicin after the first cycle, and, because of recurring complications related to their Hickman Lines, subsequent chemotherapy regimens were modified so that they received 750 mg/m^2/day of 5-FU as a 5 day infusion with their cisplatin.

Patients given magnesium on an 'as required' basis

All 14 patients had a documented episode of hypomagnesaemia on at least one occasion. 7 patients (50%) required intravenous magnesium supplements at, or before, the second cycle of ECF, and 10 patients (71%) required intravenous magnesium supplements by cycle 3. Magnesium was given in error in 3 of 71 cycles. After administration of the first cycle without magnesium in these patients, magnesium was necessary in 27 (50%) of 54 subsequent ECF cycles, and extra magnesium infusions were necessary in mid-cycle on 14 occasions (serum magnesium < 0.7 mmol/l on 3 occasions; < 0.6 mmol/l on 8 occasions, and < 0.5 mmols/l on 3 occasions).

The serum magnesium levels were already significantly lower in the 'as required' group at the time of admission for the second cycle ($P < 0.01$), and more so by the time of admission for cycle 3 ($P < 0.05$), (Table 2, Figure 1). However, there was no significant difference between magnesium levels at cycles 4, 5 and 6, although the levels were lower in the 'as required' group at cycles 4 and 5.

No patient in either group had a hypomagnesaemic fit, confusion or cardiac dysrhythmia. On many occasions, it was

Table 1. Patient characteristics in the two treatment groups

	Routine magnesium	Magnesium as required	*P* value
Number of evaluable patients	14	14	
Age	Median = 64 (range 44–72)	Median = 54.5 (range 43–75)	$P > 0.05$ (n.s.)
Baseline GFR (ml/min)	Median = 88.5 (range 60–122)	Median = 95.5 (range 54–168)	$P > 0.05$ (n.s.)
Baseline serum magnesium (mmol/l)	Median = 0.88 (range 0.69–0.92)	Median = 0.87 (range 0.79–1.12)	$P > 0.05$ (n.s.)

n.s., not significant.

Table 2. Cumulative effects of ECF chemotherapy on serum magnesium levels

On admission ECF chemotherapy	Routine magnesium	Magnesium as required	*P* value
Cycle 2	Median = 0.85 (range 0.62–1.01) (n = 11)	Median = 0.73 (range 0.6–0.88) (n = 11)	$P < 0.01$
Cycle 3	Median = 0.77 (range 0.56–0.92) (n = 10)	Median = 0.71 (range 0.45–0.82) (n = 12)	$P < 0.05$
Cycle 4	Median = 0.83 (range 0.55–0.98) (n = 9)	Median = 0.72 (range 0.59–0.82) (n = 9)	$P > 0.05$
Cycle 5	Median = 0.85 (range 0.59–0.89) (n = 5)	Median = 0.73 (range 0.61–0.87) (n = 9)	$P > 0.05$
Cycle 6	Median = 0.67 (range 0.59–0.72) (n = 3)	Median = 0.67 (range 0.59–0.71) (n = 8)	$P > 0.05$

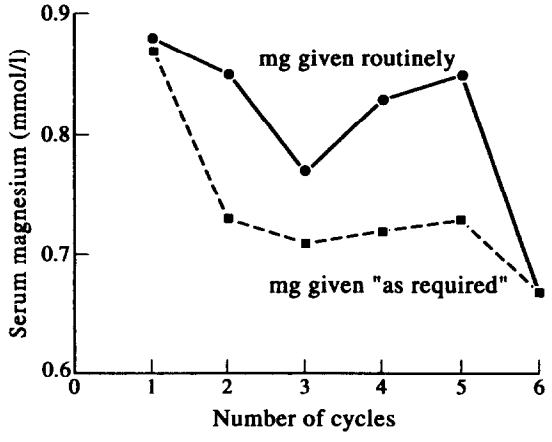

Figure 1. Plot of median serum magnesium level (mmol/l) on admission for each cycle of ECF chemotherapy for patients who received magnesium supplements routinely, and those who received supplements as required. The median serum magnesium level progressively decreased with increasing number of cycles of chemotherapy in both treatment groups, and the decrease was significantly greater in those patients who did not routinely receive magnesium, although this was only statistically significant on admission for the second and third cycles. For the number of measurements made for each point see Table 2.

difficult to determine whether symptoms such as lethargy were due to the low magnesium or related to cytotoxic chemotherapy or the malignancy. However, for the patients who received magnesium on an 'as required' basis, hypomagnesaemia was thought to be implicated as a cause of the patients' symptoms, either wholly or partly, in 24 of the hypomagnesaemic episodes, and these symptoms were predominantly of weakness and lethargy, but also included one episode of ataxia, and one episode of postural hypotension.

Patients who routinely received intravenous magnesium supplements

Of the 14 patients who routinely received magnesium supplements, 8 (57%) patients treated with a total of 37 cycles of ECF had no documented hypomagnesaemic episodes. Additional intravenous magnesium supplements were given to this group of patients on six occasions (serum magnesium < 0.7 mmol/l on two occasions; < 0.60 mmol/l on four occasions).

Of those patients with episodes of hypomagnesaemia, 1 had a marginally low magnesium level prior to his first course of ECF, and had a persistently low magnesium level throughout his chemotherapy, although he experienced no symptoms from this. One other patient developed severe 5-FU toxicity, with profuse diarrhoea, prolonged adynamic ileus (requiring total parental nutrition), and several episodes of hypomagnesaemia requiring further intravenous supplements, although it was unclear if his

symptoms were related to hypomagnesaemia or to his other medical problems. 4 other patients had documented episodes of hypomagnesaemia, although only on one occasion was this < 0.6 mmol.

Oral magnesium supplements

4 of the patients receiving magnesium as required also received oral magnesium for persistent hypomagnesaemia despite intravenous supplements, starting after three (2 patients), four and five cycles of ECF. Only the patient who developed severe 5-FU from the group receiving routine magnesium supplements toxicity received oral magnesium supplements. In all these patients, the addition of oral supplements did not prevent further episodes of hypomagnesaemia requiring additional intravenous magnesium supplements, both on admission for chemotherapy and in mid-cycle.

Cost

The cost of routine intravenous magnesium supplements (28 mmol) per cycle of ECF chemotherapy is £34.30. The 14 patients who routinely received magnesium supplements had 64 cycles of chemotherapy at a cost of £2195.20, together with an additional £78.40 for the interim magnesium infusions (£4.90 per 4 mmol). The cost per patient per cycle was therefore £35.53.

For those 14 patients who received magnesium supplements on an 'as required' basis, a total of 27 cycles were given with magnesium (cost = £926.10) and a total of 216 mmol of magnesium were given in 14 interim magnesium infusions (cost = £264.60). The total cost per patient per cycle was £17.51.

DISCUSSION

Magnesium is primarily an intracellular cation. It is an important cofactor in many intracellular enzymatic reactions, and is necessary for numerous physiological functions [24]. The plasma magnesium concentration depends mostly on tubular reabsorption of the filtered ion, although 25–65% of dietary magnesium is interstitially absorbed [25]. Cisplatin-induced renal tubular damage leads to hypomagnesaemia by causing a decrease in the maximal rate of tubular reabsorption, leading to urinary magnesium wasting [4]. Moreover, patients with low serum magnesium concentrations continue to excrete similar amounts of magnesium, presumably because they have an obligatory urinary magnesium loss [13].

Patients treated with a combination of cisplatin and 5-FU (who did not routinely receive magnesium supplements) all developed at least one episode of hypomagnesaemia, and had a significantly lower serum magnesium level on admission for subsequent cycles of chemotherapy. In the majority of cases, this had occurred by the time of admission for the third cycle. Although there was no statistical difference between the serum magnesium level on admission for the fourth and subsequent cycles of chemotherapy between the two groups, this is most likely to be due to the small number of patients still in the study at this stage. Furthermore, patients were also receiving interim magnesium supplements between cycles if hypomagnesaemic. Patients who received magnesium on an 'as required' basis also had a significantly lower mean interim serum magnesium level compared with the group who received magnesium supplements routinely.

Some 43% of those patients who routinely received magnesium supplements also had documented episodes of hypomagnesaemia, but these were not usually low enough to cause symptoms. Conversely, for those patients who were not receiving magnesium routinely, the majority had symptoms attributable to hypomagnesaemia, necessitating further magnesium infusions between chemotherapy cycles. Contrary to the findings of Vokes *et al.* [16], there was no additional benefit from giving oral supplements to patients who were persistently hypomagnesaemic despite i.v. supplements.

Although the cost of magnesium supplements used was considerably lower when given on an 'as required' basis, this does not take into account the increased number of serum magnesium assays required for patient monitoring, nor the considerable patient morbidity resulting from hypomagnesaemia, in some cases requiring hospital admission for interim i.v. magnesium supplements.

In many of the studies that have previously reported cisplatin-induced hypomagnesaemia, patients were receiving cisplatin-containing regimens for germ-cell tumours [4, 13]. Consequently, in addition to any possible synergistic effect of 5-FU with cisplatin, patients treated with ECF are usually older and are more likely to have impaired magnesium conservation due to other concomitant disorders, such as diabetes mellitus or diuretic therapy. In addition, ECF chemotherapy can cause myelosuppression, and may lead to episodes of sepsis requiring therapy with aminoglycoside antibiotics. This may exacerbate tubular damage and hypomagnesaemia, and possibly potentiate gentamicin-induced renal tubular toxicity [26]. The synergistic renal toxicity of cisplatin and aminoglycoside antibiotics may be mediated by hypomagnesaemia]26].

We conclude that all patients receiving ECF chemotherapy should be given intravenous magnesium supplements with each cycle of cisplatin chemotherapy. Nevertheless, episodes of hypomagnesaemia may still occur, and patients should have levels measured routinely prior to each cycle of chemotherapy, and if they have symptoms. Furthermore, there should be a high index of suspicion of hypomagnesaemia in patients who complain of non-specific symptoms. In documented cases of hypomagnesaemia, intravenous rather than oral magnesium supplements should be given.

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Epidermal Growth Factor Receptor (EGFr) Expression in Non-small Cell Lung Carcinomas Correlates with Metastatic Involvement of Hilar and Mediastinal Lymph Nodes in the Squamous Subtype

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Epidermal growth factor receptor (EGFr) levels were evaluated in paraffin-embedded tumour specimens of non-small cell lung cancer (NSCLC) from 176 patients who underwent surgical resection. The EGFr expression was evaluated by immunocytochemical assay using a monoclonal antibody which recognises the external domain of the receptor. EGFr immunoreactivity was significantly higher in squamous than in non-squamous cell carcinomas ($P = 0.0009$). Hilar and/or mediastinal nodal involvement was found in 29 of 105 (27.4%) squamous cancers, and in this group of patients, the mean of EGFr positive cells was significantly higher than that of patients without nodal involvement ($P = 0.01$). No significant correlations were found between the expression of EGFr and other clinicopathological or biological parameters such as T-status, grading, proliferative activity. EGFR is suggested to represent a useful indicator of nodal metastasis in NSCLC.

Key words: EGFr, NSCLC, immunocytochemistry, prognosis
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