Foscarnet (trisodium phosphonoformate hexahydrate, Foscavir) is a pyrophosphate analogue that inhibits many viral DNA polymerases (8). It is used to treat cytomegalovirus (CMV) and acyclovir-resistant mucocutaneous herpes simplex virus disease in immunocompromised patients, including those with AIDS (3, 10, 19, 27, 28, 32). Foscarnet is normally administered every 8 or 12 h as an intravenous infusion (21). Reversible nephrotoxicity is a well-recognized side effect and prehydration substantially reduces its incidence (6, 9, 17). Abnormalities of blood chemistries are also common and on occasion severe. These changes include magnesium depletion, acute ionized hypocalcemia and hypomagnesemia, hypokalemia, and hypophosphatemia (13, 15, 17–19, 23, 27, 31, 32; M. S. Youle, J. Clarbour, B. Gazzard, and A. Chanas, Letter, Lancet 1:1455–1456, 1988). The mechanisms by which foscarnet induces these changes, especially in ionized cations, are not completely understood.

As a pyrophosphate analogue, foscarnet is a potent chelator of divalent cations. Complexes readily form with calcium and magnesium in solution (17, 18, 36), and a linear relationship exists between ionized hypocalcemia, ionized hypomagnesemia, and circulating plasma foscarnet concentrations (18, 26). Chelation of free calcium and magnesium acutely reduces ionized but not total concentrations of these cations in vitro and in vivo (5, 18; E. Dohin, C. Kindermans, J. C. Souberbielle, C. Sachs, and C. Katlama, presented at Int. Conf. AIDS, 1993). Clinical symptoms associated with foscarnet-induced ionized hypocalcemia or symptoms associated with foscarnet, routine intravenous supplementation for patients with normal serum magnesium levels is not recommended during treatment with foscarnet.
reduce serum calcium through enhanced urinary excretion and by shifting calcium into cells (2, 20). We examined these relationships by intravenously injecting various doses of MgSO4 into patients with AIDS and active CMV disease who were receiving foscarnet. Acute changes in ionized blood magnesium (iMg2+) and iCa2+ were then observed. PTH levels were assayed to determine what effect, if any, MgSO4 has on parathyroid function; other side effects associated with foscarnet administration were tabulated (7; Dohin et al., Int. Conf. AIDS, 1993). Finally, this study addressed the safety of intravenous MgSO4 in this chronically ill population.

TABLE 1. Sequence across study days of MgSO4 and placebo doses for 12 subjects in a crossover design employing three replicated Latin squares

<table>
<thead>
<tr>
<th>Subject no.</th>
<th>Dose of MgSO4 (g)</th>
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<tbody>
<tr>
<td>Day 1</td>
<td>Day 2</td>
</tr>
<tr>
<td>1</td>
<td>1</td>
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<tr>
<td>2</td>
<td>2</td>
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<td>3</td>
<td>Placebo</td>
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<td>4</td>
<td>Placebo</td>
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<tr>
<td>10</td>
<td>2</td>
</tr>
<tr>
<td>11</td>
<td>Placebo</td>
</tr>
<tr>
<td>12</td>
<td>3</td>
</tr>
<tr>
<td>13†</td>
<td>3</td>
</tr>
</tbody>
</table>

* Subject no. 5 was removed from the study due to a protocol violation (dose sequence error) and reenrolled after a 2-day washout as subject no. 13 using the same dose sequence; data for subject no. 5 were excluded except those for adverse events.

RESULTS

Magnesium. Treatment groups that were administered MgSO4 prior to morning infusion of foscarnet experienced a dose-related increase in mean serum magnesium and iMg2+ levels (Fig. 1). Decreases in serum magnesium levels followed occurring foscarnet infusion in a dose-related manner. Following infusion, serum magnesium levels gradually declined toward baseline over 3.5 h, but levels remained elevated in all three active-dose groups.

Levels of iMg2+ dropped abruptly during infusion for all dose groups, so that each dose group achieved a mean value either just below (with the 3-g dose) or more substantially below the baseline by the end of foscarnet infusion. Treatment differences for the changes from baseline in mean iMg2+ concentration among the four groups were highly significant (P < 0.001) and dose related (P < 0.001). All treatment groups had similar average rates of increase in iMg2+ concentration during the 3.5 h after foscarnet infusion. In a dose-dependent manner, each MgSO4 treatment significantly (P < 0.001) reduced the magnitude of foscarnet-induced ionized hypomagnesemia at each post-foscarnet infusion assessment. By the final assess-

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ment, all active dose groups had recovered or nearly recovered to the baseline level.

**Calcium.** Mean total serum calcium values showed a slight drop after infusion of MgSO₄ or placebo (Fig. 2). This decrease was maintained throughout the period of observation and likely reflected the hydration given before foscarnet infusion. With respect to $\text{iCa}^{2+}$, all treatment groups experienced little change due to pre-foscarnet infusion hydration, followed by a substantial decrease after foscarnet infusion. At the completion of the morning foscarnet infusions, low $\text{iCa}^{2+}$ values gradually recovered but remained similar for all groups and were still below baseline after 3.5 h. No significant differences were observed among treatment or placebo groups at any assessment time.

**PTH.** MgSO₄ supplementation had no discernible effect on mean PTH levels prior to foscarnet infusion (Fig. 3). Compared to placebo, MgSO₄ administration increased mean PTH levels post-foscarnet infusion for all treatment groups ($P < 0.02$). At the immediate post-foscarnet infusion time, the placebo group mean was lower than the mean for each of the other dose groups, but the 2-g group showed greater increases in PTH than either the 1- or 3-g group, suggesting a lack of a true dose-response effect. At 1.5 and 3.5 h post-foscarnet infusion, the overall test for treatment differences and linear trends did not show significance ($P > 0.05$). The comparisons between the 2-g and placebo groups at these times, however, continued to show significance ($P = 0.05$ and 0.02, respectively). These data indicate that MgSO₄ facilitated release of preformed PTH from the parathyroid gland.

**Other laboratory values.** MgSO₄ doses had no observable effects on plasma sodium level, hematocrit, or pH (data not shown). A trend toward a lower plasma phosphate level was found at each of the three measurement intervals following foscarnet infusion. Similarly, a trend toward a lower plasma potassium level was found, but only at the 1.5- and 3.5-h postinfusion times. Changes from baseline were not statistically significantly different among the MgSO₄ dose groups at any postinfusion assessment time for either phosphate or potassium (data not shown).

**Other clinical parameters.** Symptoms associated with hypocalcemia and/or hypomagnesemia were assessed prior to,
Magnesium exists in blood in an ionized form (55%), complexed to anions such as phosphate, bicarbonate, and citrate (15%), and bound to proteins (30%). Unlike calcium, magnesium homeostasis is regulated not by hormones but instead through the direct actions of nephrons in the kidney (29, 38).

Hypomagnesemia is a common side effect of selected drugs such as foscarnet, but other causes include poor oral intake, gastrointestinal losses, kidney disease, and redistribution following trauma, burns, and cardiopulmonary bypass (14, 38). Short- and long-term clinical manifestations of magnesium depletion include muscular spasms, seizures, vertigo, ataxia, weakness, depression, electrocardiogram changes (e.g., widened QRS complex or prolonged PR interval), osteoporosis, osteomalacia, and atherosclerosis (38).

As a therapeutic agent, magnesium is used as an anticonvulsant and potent vasodilator. It has been used for prophylaxis and therapy in a variety of cardiovascular disorders, for treatment of preeclampsia and eclampsia, and to treat stroke (4, 14). Extensive clinical use has confirmed the safety of rapid administration of large doses of MgSO4. Typically, only small decreases in blood pressure are seen (14, 37), although hypertension, decreased respiration, vomiting, neuromuscular blockade, and coma have been reported (14, 30, 37).

This double-blind, placebo-controlled, randomized, crossover study sought to establish the efficacy of parenterally administered MgSO4, included with the hydration before foscarnet infusion, in preventing foscarnet-induced ionized hypocalcemia and hypocalcemia and symptoms. The study population consisted of 12 patients with AIDS, fair-to-good functional status, and active CMV disease. Overall, doses of MgSO4 reduced or eliminated foscarnet-induced acute ionized hypomagnesemia. Supplementation, however, had no discernible effect on foscarnet-induced ionized hypocalcemia despite a greater increase in serum PTH levels. The lack of effect of higher PTH levels on the fall in iCa2+ is unexplained. Perhaps there are direct or indirect effects of foscarnet, human immunodeficiency virus, or CMV on bone osteoclasts that are yet to be identified, or possibly higher PTH levels were not sustained long enough to mobilize skeletal calcium. Alternatively, a direct hypocalemia action of magnesium infusion may have offset the influence of higher PTH levels (2, 20).

MgSO4 at doses up to 3 g were generally well tolerated. No associations were detected among any MgSO4 dose and the incidence of any recorded symptoms. Significant blood pressure, pulse, or electrocardiogram changes were not noted. The lack of significant adverse events following MgSO4 infusions is consistent with other reports for patients having received equally large or larger doses of parenteral MgSO4 (4, 14). Although there was a trend toward more nervous system disorders associated with the groups receiving the higher doses of MgSO4, these signs and symptoms were associated with infusions of foscarnet, not MgSO4. These signs and symptoms are normally associated with hypocalcemia and not with hypomagnesemia or administration of MgSO4. Since parenteral MgSO4 did not alter the hypocalcemia or symptoms associated with foscarnet infusion, routine supplementation in patients with normal serum magnesium levels cannot be recommended during treatment with foscarnet.

Foscarnet is indicated for the treatment of immunocompromised patients with CMV or acyclovir-resistant mucocutaneous herpes simplex virus disease (19, 27, 28, 32). Nephrotoxicity and electrolyte abnormalities are the most common adverse side effects associated with its use. In this study only a single case of reversible nephrotoxicity occurred among the 12 subjects (8%). This percentage is comparable to the 15 to 20% incidence of nephrotoxicity per year reported in a recent large controlled trial (35). Electrolyte abnormalities following fos-
carnet infusion include acute ionized hypocalcemia and hypomagnesemia, hypokalemia, and hypo- or hyperphosphatemia. While these changes are often self-limited, serious adverse sequelae can occur, including seizures, arrhythmias, paresthesias, and changes in the sensorium (13, 17, 18, 24, 34; Youple et al., Letter). In this study foscarnet-associated symptoms were infrequent, and MgSO₄ appeared to be of no benefit in preventing them.

Several limitations should be considered while interpreting these data. First, this study was short-term, lasting only for 4 days. Long-term effects of parenteral MgSO₄ administration on blood calcium, magnesium, or PTH levels cannot be inferred from these data. Second, the failure to detect any effect of MgSO₄ on the fall in iCa²⁺ concentrations following foscarnet infusion was perhaps due to inadequate dosing. Other studies have used substantially higher MgSO₄ doses to achieve >3-fold increases in blood magnesium concentrations compared to baseline values (14, 16, 37). The maximal dose of MgSO₄ used in this study, however, did not quite double the mean serum magnesium concentrations (Fig. 1). Any concern for inadequate dosing should be considered in light of the fact that the 3-g MgSO₄ dose returned post-foscarnet infusion iMg²⁺ levels to baseline values, and maximal rises in PTH occurred with the 2-g but not 3-g doses of MgSO₄.

Latin square designs for crossover studies, while attractive because of their inherent efficiency, have potential limitations (25). This method permits studies using relatively few subjects. A parallel-group design for three doses of MgSO₄ and placebo most likely would have required at least 48 subjects. Recruitment of this number of patients with AIDS and active CMV infection would have required screening at least 100 subjects in a multicenter trial. Instead, the Latin square crossover design allowed a pilot study to be completed at one center in a short time frame. This crossover design assumes the dose sequence for MgSO₄ and placebo does not in and of itself produce time frame. This crossover design assumes the dose sequence for MgSO₄ and placebo does not in and of itself produce significant effects. This assumption was considered valid because washout intervals between MgSO₄ doses were expected to be short in patients with normal renal function, due to rapid clearance of intravenous magnesium. The return of magnesium, calcium, and PTH levels to baseline each morning before subsequent MgSO₄ or placebo doses supported this notion.

Subjects’ medical conditions while on treatment are a potential confounder in this analysis. The influence of medical condition on outcome measures could present a serious problem in interpretation if this were a parallel study in which levels of underlying disease were not uniformly distributed across treatment groups. Using the Latin square design over a short (4-day) period, the underlying medical condition of each subject is likely to have been essentially the same during exposure to each treatment. Indeed, only one subject who developed renal insufficiency on the protocol had a significant change in medical condition during the course of the study.

The infusion of MgSO₄ modulated the hypomagnesemic effect of foscarnet in a dose-dependent manner. MgSO₄ also increased mean PTH levels, apparently restoring the sensitivity of parathyroid cells to the ionized hypocalcemic stimulus, but not in a dose-related fashion. Despite these findings, supplementation with MgSO₄ at these doses had no discernible effect on acute ionized hypocalcemia induced by foscarnet. No dose-related, clinically significant adverse events were found, suggesting that intravenous supplementation of magnesium sulfate at doses up to 3 g over 1 h is safe in this chronically ill population. However, given the lack of benefit of parenteral MgSO₄ in reducing ionized hypocalcemia or symptoms associated with foscarnet infusion, routine supplementation in individuals who have normal serum magnesium levels cannot be recommended. Given the difficulty of administering parenteral calcium, further studies using combinations of oral calcium, magnesium, and vitamin D are needed to identify regimens that might minimize ionized hypomagnesemia and hypocalcemia following foscarnet infusion.

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REFERENCES


