Gallium Nitrate for Acute Treatment of Cancer-related Hypercalcemia: Clinical Pharmacological and Dose Response Analysis

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ABSTRACT

Current treatment of cancer-related hypercalcemia is limited by agents of limited effectiveness or excessive toxicity. Gallium nitrate is a new drug which both inhibits bone resorption and increases calcium content of bone. We have now treated 39 episodes of hypercalcemia with gallium nitrate administered as a continuous i.v. infusion for 5-7 days at 3 daily dose levels (100 and 200 mg/m², and 50 mg/m² by brief infusion followed by 150 mg/m²). Nadir calcium values were significantly lower (9.2 ± 1.5 mg/dl) for patients who received the highest dose relative to patients who received the lowest dose (10.5 ± 1.6 mg/dl, P < 0.001). While the actual percentage of patients who achieved normocalcemia was higher at the highest dose relative to the lowest dose (86 versus 60%), this difference was not statistically significant. Mean serum concentration of inorganic phosphorous declined significantly for all patients from 2.9 ± 0.86 mg/dl at base line to 1.8 ± 0.66 mg/dl (P < 0.001). Pharmacokinetic studies suggested that a threshold plasma gallium concentration of approximately 1 μg/ml must be attained to achieve acute normalization of elevated serum calcium levels. Steady-state plasma gallium levels were attained after 48 h; there was no evidence of drug accumulation in plasma after 2 days. Effects on serum creatinine concentration were negligible, and there were no other toxic reactions. These data confirm preclinical experiments which suggested that inhibition of bone resorption by gallium nitrate is dependent upon the dose and duration of drug exposure. We conclude that gallium nitrate is effective treatment for cancer-related hypercalcemia. The drug is now being evaluated against standard treatment in a randomized, double-blind trial.

INTRODUCTION

Cancer-related hypercalcemia is a substantial problem in the clinical management of patients with cancer. Almost one-half of women with metastatic breast cancer eventually develop hypercalcemia at some point (1). The particular mechanisms which accelerate bone resorption are controversial (2). However, osteolysis ultimately causes excessive release of skeletal calcium into the circulation which overwhelms renal excretory capacity. Serum calcium increases with consequential morbidity such as nausea, dehydration, stupor, and coma.

Conventionally, it has been assumed that cancer-related calcium can best be controlled by achieving control of the underlying malignant disease. However, new drugs have been discovered which are potent inhibitors of bone resorption and which have no direct antitumor activity. Such agents include the biphosphonates (3-5), WR-2721 (6), and gallium nitrate (7-9). In a pilot study, we found that gallium nitrate was effective treatment for cancer-related hypercalcemia (7). This agent directly inhibits calcium release from bone (8). Unlike mithramycin, these effects are achieved without causing toxicity to bone cells (9).

This study extends our original observations to evaluate dose-response in patients with cancer-related hypercalcemia and to assess plasma gallium levels achieved after administration by i.v. infusion.

MATERIALS AND METHODS

Patient Eligibility. Patients were eligible for treatment with gallium nitrate after they had been hospitalized and aggressively treated for hypercalcemia for at least 48 h. Treatment included hydration with i.v. normal saline and furosemide-induced diuresis. Phosphates and corticosteroids p.o. were allowed if the dose was stable or decreasing. Cytotoxic chemotherapy, radiation, and mithramycin were not allowed within 7 days preceding entry nor at any time during the study. Other study requirements included: total serum calcium ≥12.0 mg/dl after rehydration and furosemide-induced diuresis; serum creatinine ≤3.0 mg/dl; maintenance of urinary output >2000 ml/day. There was no restriction upon histological cancer diagnosis. All but one patient (with non-small cell lung cancer) had previously received chemotherapy and/or radiation, and all had developed progression of the underlying disease.

Gallium Nitrate Treatment. The prescribed dose of gallium nitrate was diluted in 1000 ml of 5% dextrose solution and infused i.v. over 24 h using an infusion pump (IVAC, Inc., San Diego, CA). Patients were treated at one of three dose levels: 100 mg/m²/day for 5 days; 200 mg/m²/day for 5-7 days; and 50 mg/m² by 4-h infusion on Day 1 followed by 150 mg/m²/day for 5 days. This study was designed specifically to assess the ability of gallium nitrate to achieve acute normalization of elevated serum calcium levels. Maintenance of normocalcemia was not an objective, although patients could be retreated with subsequent infusions of gallium nitrate for recurrent episodes of hypercalcemia.

Pharmacokinetic Study. Approximately 10 ml of blood were drawn into heparinized glass tubes at base line and at specified times during the drug infusion. Whole blood was centrifuged at 180 × g to separate plasma from RBC. The plasma was frozen in plastic tubes at 0°C until analyzed. Gallium concentration was measured by flameless atomic absorptiometry using a method with minor modifications which we have previously described (10). Plasma gallium levels were also determined in 4 normocalcemic patients who received gallium nitrate (200 mg/m²/day) for 7 days as part of a study of patients with bone metastases (11). Pharmacokinetic data from these patients are reported in this study.

Patient Monitoring. The following tests were performed prior to entry into the study: total serum calcium; serum albumin; serum inorganic phosphorous; 12-channel automated biochemical profile; blood urea nitrogen; and creatinine. The presence or absence of bone involvement by tumor was assessed by skeletal scintigraphy or roentgenograms. Total serum calcium, blood urea nitrogen, and creatinine concentrations were measured daily during the drug infusion and for several days thereafter (along with inorganic serum phosphorous concentration) to determine the duration of normocalcemia and any potential drug-related toxicity. Total serum calcium was adjusted for serum albumin concentration using the formula: corrected calcium (mg/dl) = measured calcium (mg/dl) − serum albumin (g/dl) × 4.0 (12). Patients were also monitored for any other evidence of antitumor effects.

Data Analysis and Report. As with any agent, the effects of concomitantly administered therapy are potentially confounding factors in the analysis of response and toxicity. In this paper, these parameters are specifically defined. Concomitant administration of p.o. phosphorous...
or corticosteroids was allowed only if the dose was stable or decreasing. Introduction of hypocalcemic medication(s), cytotoxic chemotherapy, or radiation (even if localized) was a protocol violation which made that treatment course ineligible for response. The duration of normocalcemia was defined as that period after normalization of serum calcium up to the day of recurrent hypercalcemia, hospital discharge without follow-up determinations of serum calcium, or (most commonly) the administration of other antitumor or hypocalcemic treatment (including p.o. phosphorous or corticosteroids). In view of these factors, the reported durations of normocalcemia may underestimate the hypocalcemic effect of gallium nitrate in many patients. Similarly, the evaluation for potential drug-related toxicity (particularly effects on serum creatinine and phosphorous) includes data obtained up to the day of recurrent hypercalcemia, administration of chemotherapeutic or hypocalcemic medications, or a maximal period of 2 wk after completing the drug infusion if none of these conditions applied. Data are presented as median values or as the mean ± SD. Two-sided t tests were used for statistical analysis of differences between means.

RESULTS

Patient Entry. Forty-five infusions of gallium nitrate were administered to 36 individual patients. Thirty-nine treatment courses in 31 patients are considered fully evaluable for hypocalcemic response. The median age of the evaluable patients was 50 yr (range, 21–72); the median Karnofsky performance status was 40 (range, 20–70). There were 20 males and 11 females. Six treatment courses were considered ineligible. Four patients received ≤3 days of treatment and were removed from the study because of clinical deterioration which was not drug related. Major protocol violations occurred in 2 other patients. One patient with lymphoma received an injection of dexamethasone on Day 5, and one patient with head and neck cancer was started on radiation therapy during the drug study. We did not attempt to quantify the extent of bone metastases other than to note presence or absence (Table 1).

Hypocalcemic Response. Gallium nitrate proved highly effective in normalizing elevated serum calcium (Table 1). The mean nadir calcium value at the highest daily dose of 200 mg/m² (9.2 ± 1.5 mg/dl) was significantly lower than the nadir value at the lowest daily dose of 100 mg/m² (10.5 ± 1.6 mg/dl) (Table 1; P < 0.001). The percentage of patients who achieved normocalcemia was also higher at the high dose level (86%). However, the difference relative to the percentage of control at the low dose (60%) was not statistically significant. Given the inherently high rate of control, a trial of approximately 60 fully evaluable patients would be required to detect this difference with 95% confidence (power = 0.8). Improved clinical response at the highest dose level (manifested by more rapid control for more prolonged duration) was observed in several patients treated with sequential gallium infusions for recurrent episodes of hypercalcemia. Representative curves from 2 of these patients are shown in Fig. 1.

Duration of normocalcemic control was more difficult to ascertain. Largely, this difficulty was due to the subsequent administration of other cytotoxic chemotherapy or radiation which (as defined above) terminated the hypocalcemic effect which could be clearly ascribed to gallium nitrate. Any such treatment may have uncertain effects upon tumor and/or bone cell function. The durations of response noted in Table 1 as "+" days indicate the administration of other therapy and thus may underestimate the hypocalcemic effects of gallium. Infusions in 9 patients who received the highest dose (200 mg/m²/day and who developed recurrent hypercalcemia without intercurrent treatment maintained normocalcemia for a median duration of 8 days (range, 5–14 days). At the lowest dose (100 mg/m²/day), the median duration of normocalcemia without other treatment was 6 days (range, 4–12 days; n = 4).

One patient with malignant lymphoma experienced transient regression of an abdominal mass coincidently with this treatment. She subsequently developed obviously progressive disease and who developed recurrent hypercalcemia without intercurrent treatment maintained normocalcemia for a median duration of 8 days (range, 5–14 days). At the lowest dose (100 mg/m²/day), the median duration of normocalcemia without other treatment was 6 days (range, 4–12 days; n = 4).

One patient with malignant lymphoma experienced transient regression of an abdominal mass coincidently with this treatment. She subsequently developed obviously progressive disease without recurrence of hypercalcemia. No other antitumor activity was observed in this study.

Pharmacokinetic Analysis. Detailed blood sampling was performed during 15 drug infusions administered over 5 days for treatment of hypercalcemia. Blood sampling was performed in 4 other normocalcemic patients who received gallium nitrate at 200 mg/m² for 7 days. Plasma gallium concentrations for all 19 infusions are reported.

As noted in Fig. 2A, the daily dose level of 200 mg/m²/day
achieved steady-state plasma gallium concentrations between 1.0 and 1.5 μg/ml after 48 h in all hypercalcemic patients. The intermediate dose level of 150 mg/m²/day, preceded by a brief i.v. infusion of 50 mg/m², produced consistently lower plasma concentrations (Fig. 2). Moreover, the brief infusion did not appreciably shorten the time to reach steady-state concentrations (Fig. 2A). This dose level was abandoned after the entry and pharmacokinetic study of 4 patients (one of whom was invaluable for hypocalcemic response due to a concurrent dexamethasone injection). Two of the 3 evaluable hypercalcemic patients treated at the 50 plus 150 mg/m² level failed to achieve normocalcemia. There was no evidence of drug accumulation in plasma beyond 72 h after initiation of the continuous i.v. infusion at any dose level.

Although the mean nadir calcium value was significantly lower after administration of the 200-mg/m² daily dose, the percentage of patients who achieved normocalcemia relative to the 100-mg/m² daily dose was not significantly different. Five patients underwent detailed blood sampling at the lowest dose level. Only one of these 5 patients failed to achieve normocalcemia. As noted in Fig. 2B, plasma gallium concentrations were consistently lower in this individual during the entire duration of the drug infusion relative to the other patients sampled. Patients who achieved normocalcemia at the lowest dose level also attained a plasma gallium concentration ≥0.95 μg/ml, whereas the individual with uncontrolled hypercalcemia failed to attain a plasma level >0.45 μg/ml at any time. This individual had compression of the superior vena cava from an extrinsic mass; however, the infusion was administered without difficulty through a central venous catheter. The reason(s) for the substantially lower plasma gallium concentrations in this case is unexplained. Two patients treated at a dose of 100 mg/m² had plasma gallium concentrations of 0.2 and 0.14 μg/ml detected 8 and 11 days later when they developed recurrent hypercalcemia.

Toxic Reactions. Gallium nitrate was well tolerated. Several patients had preexisting gastrointestinal complaints (nausea, constipation) which were ascribed to hypercalcemia or concurrent use of narcotic medication. The effects of gallium on renal function were evaluated by recording the highest and lowest values of serum creatinine measured on study relative to the initial value. In 15 of 39 treatment courses, the base-line creatinine was the highest value recorded. In the 21 evaluable infusions at the 200-mg/m² daily dose, the median increase from base line to peak serum creatinine was 0.2 mg/dl; the median increase at the 100-mg/m² daily dose (n = 15) was 0.1 mg/dl. The median decrease from base-line serum creatinine to nadir was 0.2 mg/dl at the highest level; the median decrease at the lowest level was 0.3 mg/dl. The highest value recorded for any patient was 2.7 mg/dl which was identical to the highest initial value. The effect of gallium upon creatinine clearance could not be accurately determined. The confused and stuporous condition of many patients at entry resulted in a large number of inadequate urine collections.

The observed differences in hypocalcemic effect between the high and low dose groups were not due to differences in renal function. Mean serum creatinine concentrations (±SD) at base
calcemia. One patient received p.o. calcium replacement on a decrease in serum concentration of inorganic phosphorous. Serum phosphorous concentration in all 39 patients declined from a mean value of 2.9 ± 0.86 mg/dl at base line to a nadir value of 1.8 ± 0.66 mg/dl (P < 0.001). Fluid intake was retrospectively assessed for the period immediately preceding gallium treatment and daily during the drug infusion. There was no significant difference between mean daily fluid intake for all patients before or during therapy (3750 versus 3640 ml/day, respectively). Mean daily fluid intake during therapy for patients who achieved normocalcemia at the lowest dose level was similar to patients who did not respond (5370 versus 4992 ml/day, respectively). Thus, it is not likely that the observed hypocalcemic effects occurred simply as a result of hydration and diuresis.

**DISCUSSION**

The current study confirms preliminary findings of the effectiveness of gallium nitrate for acute control of cancer-related hypercalcemia (7). It is apparent from these data that normocalcemia can be achieved with minimal toxicity and that the effect occurs independently from other antitumor activity. In *vitro* studies suggested that gallium-induced inhibition of calcium release from bone was dependent upon drug concentration (7). We noted a trend in favor of improved control for longer duration at the highest dose level and a highly significant difference in the mean lowest calcium value relative to the low dose (Table 1; Fig. 1). The *in vitro* effects were also dependent upon the duration of exposure to the drug (7). Most patients in this study did not manifest a decline in serum calcium until 48 h after initiation of treatment which approximates the time at which steady-state concentrations were attained (Fig. 2). Eleven of 12 drug infusions in fully evaluable hypercalcemic patients which resulted in normocalcemia were also associated with a plasma gallium level ≥0.92 μg/ml at 72 h. Two infusions in patients who developed recurrent hypercalcemia after prior therapy with gallium both had plasma gallium concentrations <0.2 μg/ml. Therefore, it appears likely that a threshold plasma gallium level of approximately 1 μg/ml must be attained in order to acutely normalize elevated serum calcium.

Gallium is incorporated into bone at mg levels (per mg of bone mineral) (8). Therefore, plasma gallium concentrations represent only one aspect of a complex pharmacodynamic equilibrium. Laboratory data suggest that optimal effects upon bone resorption are achieved with prolonged treatment at low doses. Thus, the lowest dose examined in this study probably exceeds the amount necessary to maintain a normocalcemic state, especially since almost half of these patients developed frank hypocalcemia (Table 1). We have elected to use a dose of 200 mg/m² for 5 days by infusion in current studies. This dose is less than 50% of the Phase II anticancer dose (13, 14).

The mechanisms which cause hypercalcemia in cancer patients are multifactorial and controversial. Although good evidence exists for humoral or nonhumorally mediated mechanisms (15), true “ectopic” production of parathyroid hormone probably occurs only as a rare event (16). We elected not to intensively explore potential mechanisms of hypercalcemia in this study since our data indicated that gallium nitrate directly inhibits bone resorption. Gallium exerts at least 2 major effects upon bone. (a) X-ray diffraction studies of hydroxyapatite taken from bones of gallium-treated rats show that these crystals are larger in size or more perfect than crystals from untreated animals (9). Such crystals are less soluble and therefore less susceptible to dissolution. (b) *In vivo* treatment with gallium nitrate increases the calcium content of rat bones relative to untreated controls (9). Unlike other drugs used for the treatment of hypercalcemia (e.g., mithramycin), these effects are not associated with toxicity to bone cells (9). Furthermore, treatment with saline hydration and diuretics enhances further calcium release from bone. Therefore, most conventional treatment ultimately weakens the strength of already compromised bone.

Recently, several new agents have been discovered which directly affect the fundamental disorder in hypercalcemia, namely, accelerated osteolysis and increased skeletal mobilization of calcium. Such agents include gallium nitrate, WR-2721, and the biphosphonates.

WR-2721 is a new compound which was originally developed as a chemoprotective drug. Subsequently, this agent was found to cause hypocalcemia by inhibiting secretion of parathyroid hormone and also by decreasing bone resorption (17, 18). Evidence of activity in hypercalcemic patients appears definite (13), although large-scale trials have not been reported. An extensive literature exists with respect to the biphosphonates. The best-studied drug, dichloromethylene diphosphonate (clodronate), has demonstrated activity in clinical trials (3, 4). However, this compound has been withdrawn from clinical use pending further evaluation of potential delayed toxic effects (secondary leukemias). A new biphosphonate, aminoxypropyldiene diphosphonate, has been successfully tested in two European trials (5, 19). The drug has controlled patients with hypercalcemia after a variable number of daily i.v. infusions. However, a recent randomized trial showed that median calcium values in hypercalcemic patients treated with aminoxypropyldiene diphosphonate remained above normal despite 9 daily infusions (20). Therefore, the potency of this agent remains uncertain.

Each of these new compounds appears to be well tolerated at doses which are effective for the acute management of hypercalcemia. The exact duration of normocalcemic control induced by these drugs has been difficult to assess for reasons noted in this study. Clearly, maintenance of a normocalcemic state is preferable to treatment of recurrent episodes of hypercalcemia. Given these considerations, a route other than i.v. infusion would be desirable for long-term management. Sensitive measurements (enzymuria and renal excretion of β2-microglobulin) have shown that high-dose infusions of gallium nitrate are not associated with chronic nephrotoxicity (14). We have demonstrated excellent bioavailability of gallium in blood and bone after s.c. injections of gallium nitrate in rodents. These data suggest that s.c. injections of gallium administered every 24–48 h may be sufficient to maintain normocalcemia. A clinical-pharmacological study of the s.c. route is expected to begin in the near future.

Finally, it must be noted that none of these new compounds has yet proven to be clinically superior to aggressive conventional management of cancer-related hypercalcemia. Therefore, evidence for their efficacy must be regarded as preliminary regardless of proposed theoretical advantages. A randomized, double-blind trial of gallium nitrate versus standard therapy has been initiated.

3 R. Warrell et al., unpublished data.
GALLIUM NITRATE IN HYPERCALCEMIA

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