Pharmacokinetic and Toxicity Evaluation of Five-Day Continuous Infusion versus Intermittent Bolus cis-Diaminedichloroplatinum(II) in Head and Neck Cancer Patients


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ABSTRACT

We administered cis-diaminedichloroplatinum(II), 30 mg/m²/day for 5 days by continuous infusion to six patients with head and neck cancer, and compared the total and filterable plasma concentrations of platinum, and toxic effects, with those observed in five additional patients who received the same dose and schedule of cis-diaminedichloroplatinum(II) by intermittent bolus. In the continuous infusion group, the total 5-day exposure to filterable platinum, determined from the area under the concentration-time curve, was 1.5 to 2-fold higher (P < 0.01) than that observed in the intermittent bolus group although the maximum filterable platinum concentration achieved was 8-fold lower (P < 0.01). These differences were not reflected by total platinum levels. Subclinical nephrotoxicity, as judged by monitoring the urinary excretion of the renal enzymes N-acetyl-β-D-glucosaminidase and alanine aminopeptidase, as well as ototoxicity, and the incidence and severity of nausea and vomiting were similar in both groups. In contrast, myelosuppression, and hypomagnesemia were more frequent in the continuous-infusion patients, suggesting that the total exposure to free platinum contributes more to these toxicities than peak levels achieved. Considering the clinically acceptable toxicity observed after administration by continuous infusion, we recommend larger therapeutic trials to define the efficacy of increased tumor exposure to filterable platinum.

INTRODUCTION

Cisplatin is one of the most active agents available for the treatment of solid tumors, in particular, head and neck (1), testicular, and ovarian cancers (2). In clinical trials the common method of administration is either a large single bolus or daily bolus dosing. The dose-limiting toxicity is acute renal tubular damage which is reduced by using hydration and forced diuresis (3) or a vehicle with high chloride ion concentration (4, 5). These maneuvers however, offer no protection against neurotoxicity, ototoxicity, myelosuppression, and nausea and vomiting. In a previous trial conducted at the University of Michigan, we administered cisplatin in a dose of 50 mg/m²/day for 4 days or 40 mg/m²/day for 5 days as a bolus to advanced head and neck cancer patients. We observed a 73% response rate, double that expected from single-agent cisplatin. However, cumulative toxicities limited treatment to two or three courses in the majority of patients (6).

The active platinum species is nonprotein-bound or filterable platinum (7). In vitro data suggest that prolonged low dose exposure may be advantageous for increasing cell kill and reducing toxicity (8). Since our data and that of others support a dose-response effect for cisplatin (4, 6, 9), an important question is whether the therapeutic index can be improved by using an alternate method of administration. Therefore, we conducted a trial directly comparing the pharmacokinetics of bolus and continuous infusion cisplatin in the treatment of a responsive tumor, head and neck cancer. The specific objectives were to determine the exposure to filterable cisplatin for each method of drug administration as measured by the product of drug concentration x time (AUC) and to determine the toxic effects.

MATERIALS AND METHODS

Patients

All patients had a histologically confirmed diagnosis of squamous cell carcinoma of the head and neck, either recurrent disease or newly diagnosed Stage IV cancer. Patients with prior exposure to cisplatin were excluded; however, they may have had other chemotherapy or radiation therapy not less than 4 weeks prior to study entry. All patients had bidimensionally measurable disease, a Karnofsky performance status of at least 60%, a life expectancy of at least 12 weeks, adequate bone marrow reserve (WBC > 3500 cells/μl, platelets > 100,000 cells/ml), adequate renal function (creatinine clearance ≥ 60 ml/min, serum creatinine < 2 mg/dl), normal sensorimotor neurological exam, and audiometry. If a hearing loss was present, this could not exceed 30 dB at 500, 1000, and 2000 Hz. There was no age limitation. However, patients over 70 were required to have a performance status of at least 70% and a creatinine clearance of at least 80 ml/min. All patients gave informed consent in accordance with institutional guidelines.

Patients were alternately assigned to treatment with either CI or IB cisplatin in a dose of 30 mg/m²/day for 5 days. There was no attempt to balance the two treatment groups with regard to prior treatment or extent of disease. Pre- and posttreatment hydration were identical for both groups. This consisted of 500 ml of normal saline over 2 h prior to the start of cisplatin on Day 1 and 500 ml of normal saline with 20 meq KCl over 2 h followed by 500 ml DSW with 4 g MgSO₄ over 2 h at the completion of cisplatin on Day 5. CI cisplatin was started at 7:00 a.m. on Day 1. The total daily dose of 30 mg/m² was divided in 3 liters of normal saline and infused at 125 ml/h over each 24-h period for 5 days. IB cisplatin was administered as 30 mg/m² in 150 ml normal saline over 20 min, from 4:40 p.m. to 5:00 p.m., daily for 5 days. Between cisplatin doses normal saline was infused at 125 ml/h. No diuretics were administered to either group unless patients showed signs of fluid overload. Antiemetics were not given prophylactically. Thiethylperazine maleate (Torecan) was administered for nausea only if signs of fluid overload. Antiemetics were not given prophylactically. Thiethylperazine maleate (Torecan) was administered for nausea only.
assessment of measurable disease parameters. Laboratory studies included 24-h creatinine clearance, serum electrolytes, BUN, creatinine, complete blood count and platelet count. During treatment patients were monitored with daily electrolytes, BUN, and creatinine determinations. Between treatments complete blood count and differential, platelet count, serum electrolytes, creatinine, and magnesium were determined weekly. Dose adjustments were based on the nadir counts of the preceding course. A 75% dose was given if the nadir WBC count was less than 1500 cells/µl or the nadir platelet count was less than 50,000 cells/µl. Patients were removed from study if the creatinine clearance decreased to less than 60 ml/min, grade 2 or greater neuropathy occurred (absent deep tendon reflexes, motor weakness, and peripheral nerve pain), a symptomatic high frequency hearing loss or any hearing loss in the speaking range occurred, or progressive disease was documented. Standard response criteria were used (10).

**Pharmacokinetic Determinations**

**Sample Collection/Preparation.** Blood samples for the pharmacokinetic evaluation of CI cisplatin were drawn in heparinized tubes at times 0, 3, 24, 48, 72, 96, and 120 h during infusion and 15, 30, 45, 60, and 120 min after the infusion was stopped. For the IB cisplatin group, samples were drawn on Days 1, 3, and 5 at 0, 15, 30, 45, 60, 120, and 240 min, where time 0 represented the end of the 20-min bolus infusion.

24-h urines were collected and monitored for platinum excretion for each 24-h period during the 5-day continuous infusion and the 5-day intermittent bolus administration.

For analysis of the filterable (i.e., nonprotein-bound) platinum concentrations in plasma, all samples were immediately centrifuged and duplicate 2-ml portions of the resultant plasma were removed and centrifuged at 1000 x g for 1 h in CF50A Centriflow membrane cones (Amicon Corporation, Danvers, MA) to obtain filterable platinum. Total platinum was analyzed by using an aliquot of unfiltered plasma. Samples were stored at −20°C until analyzed, usually a time period of a few weeks.

**Plasma Analyses.** Unfiltered plasma samples were diluted fourfold with 10% HCl (v/v) and these were analyzed directly at 306.4 nm in a Spectrascan III (Applied Research Laboratories, Sunland, CA), a conventional d-c argon plasma emission spectrometer. Calibration standards (0.0, 0.5, and 1.0 mg/liter) were made up in plasma from hospital patients not on cisplatin therapy and these standards were also diluted fourfold with 10% HCl (v/v). The lower detection limit for platinum in unfiltered plasma, defined as three times the standard deviation of the platinum blank (11, 12), is 0.10 mg/liter (CV = 33% at detection limit; CV = 3.3% at 1.0 mg/liter).

Filterate portions, because of their low volumes (0.7 ml) and low platinum concentrations (down to 0.030 mg/liter), were analyzed without dilution and by taking the amplified emission signal directly from the instrument to a recorder, thus avoiding time delays which are present when the microprocessor operates on the signal. A single analysis using full instrumental sensitivity and a sample volume as low as 0.5 ml is accommodated with this technique. [Pt]total was analyzed at 306.4 nm and calibration standards (0.00, 0.10, and 0.20 mg/liter) were prepared by standard addition of the appropriate amount of a 100 mg/liter platinum stock solution to filtrate samples from hospital patients not on cisplatin therapy.

Urine specimens were obtained before and daily for 2 weeks with each course of cisplatin. Urinary concentrations of NAG, AAP, and total urinary protein were determined by automated spectrophotometric methods (14, 15). Enzyme and protein concentrations were expressed relative to the concentration of urinary creatinine to account for variations in urine output (16).

**Results**

**Pharmacology.** The pharmacokinetic parameters determined for both patient groups are summarized in Table 1. The maximum total platinum was similar for CI and IB; however, maximum filterable platinum was approximately eight times higher for IB (P < 0.01). The filterable platinum exposure for the 5 days as measured by area under the concentration-time curve (AUC) was increased approximately 1.5-fold by CI administration, 9.2 ± 2.5 mg h/liter compared to 6.5 ± 0.9 mg h/liter for IB, P = 0.01. This represents the minimum difference in exposures and likely underestimates the actual increase in AUC resulting from CI. This is due to the maximum steady state level of 0.02 mg Pt/liter used in the estimation of the secondary elimination phase occurring beyond the 4-h period in which plasma specimens were obtained. Without an estimation of secondary elimination, the filterable platinum exposure for IB becomes 4.4 ± 0.9 mg h/liter (range, 3.0–5.8) which results in a 2-fold increase in exposure for CI administration. Thus the minimum increase in exposure using CI compared to IB is 1.5-fold and the maximum 2.0-fold. In using only a single-kinetic elimination term in the data evaluation, half-lives for filterable

| Table 1 Summary of plasma pharmacokinetic parameters |
|------------------|------------------|------------------|------------------|
|                   | Continuous        | Interimt        |
|                   | infusion          | bolus           |
| No. of patients   | 6                | 9               |
| No. of courses    | 11               | 9               |
| Maximum [Pt]total | 1.9 ± 0.3* mg/liter | 2.1 ± 0.6  mg/liter | P = 0.05 |
| (1.5-2.5)         | (1.1-3.0)        |                 |
| Maximum [Pt]filterable | 0.10 ± 0.03 mg/liter | 0.85 ± 0.19  mg/liter | P < 0.01 |
| (0.06-0.15)       | (0.50-1.15)      |                 |
| [Pt]filterable exposure | 9.2 ± 2.5  mg h/liter | 6.5 ± 0.9  mg h/liter | P < 0.01 |
| (6.1-12.8)        | (5.1-7.8)        |                 |
| Half-life [Pt]filterable | 122 ± 74 min | 36 ± 6 min | P < 0.01 |
| (32-289)          | (23-47)          |                 |

* Mean ± standard deviation. Numbers in parentheses, range.
platinum elimination were significantly longer for the CI schedule.

The mean plasma concentrations of total and filterable platinum for the 11 courses administered by CI are illustrated in Fig. 1. Samples were obtained over the 120 h of infusion and for 2 h after the infusion ended. There was a significant linear trend using a repeated measures analysis of variance for increase in total platinum over time, $P = 0.001$, and for increase in filterable platinum, $P = 0.001$ during the continuous infusion. These data indicate an accumulation in plasma of filterable platinum. In addition a prolonged half-life of filterable platinum, $122 \pm 74$ min was observed. Since the maximum filterable platinum levels with CI are significantly lower than those with IB, the decrease of the cisplatin complex with its 30-min half-life is not the unique major process as is observed with biphasic IB elimination. A pharmacokinetic evaluation using a singleelimination term results in a longer half-life due to the important contribution of the slower tissue redistribution/elimination processes. A biphasic or multiphasic analysis was not applied because of the limited postinfusion data which were close to the analytical detection limit. In comparison, Fig. 2 illustrates the mean plasma concentrations of total and filterable platinum over 240 min after bolus administration. The data are derived from 27 bolus doses. The half-life of filterable platinum was $36 \pm 6$ min. Filterable platinum decreased more rapidly than total platinum indicating a high degree of protein binding associated with early rapid renal excretion of filterable platinum. This rapid decrease in filterable platinum would in part account for the lower total exposure over the 5 days of treatment compared to CI. Pharmacokinetic parameters were obtained for Days 1, 3, and 5 of the IB group (Table 2). There was a significant increase in the maximum total platinum measured over these 5 days ($P = 0.02$); however, maximum filterable platinum, half-life of filterable platinum, and exposure did not vary significantly. The percentages of platinum excreted in the urine for the 5-day period was $24 \pm 8$% for CI and $14 \pm 6$% for IB, $P < 0.01$. This increase in the percentage of platinum excreted in the urine in the CI patients is consistent with the increase in filterable plasma platinum concentration over time (AUC) since only nonprotein-bound platinum species are filtered by the kidney. Intercycle platinum excretion did not change between cycles 1 and 2 for IB patients ($15\%$ excreted for the 5-day period), however the platinum excretion decreased from $27 \pm 7\%$ for cycle 1 to $21 \pm 7\%$ for cycle 2 for CI patients ($P = 0.3$).

Response and Toxicity. In this series of 11 patients, eight were newly diagnosed and three had recurrent disease, only one of which had received prior chemotherapy. Six patients received 15 courses of CI cisplatin (three patients, two courses; three patients, three courses) and five received 11 courses of IB cisplatin (four patients, two courses; one patient, three courses). Recurrent disease patients were treated until progressive disease was documented. Newly diagnosed patients received definitive local treatment with surgery and/or radiation therapy after three courses if complete or partial regression of disease occurred or after two courses and disease stabilization only. Responses were observed in four (one complete, three partial) or six treated by CI and there were two partial responders of five treated by IB. Although there was a trend for more responses in the CI group, the numbers of patients were too small for a meaningful statistical analysis.

Toxicities are detailed in Table 3. Leukopenia occurred more frequently in CI patients. Prolonged myelosuppression resulted in treatment delays in four CI patients compared to none of the IB patients. Three patients (one IB, two CI) had dose reductions due to low nadir counts. This resulted in $75\%$ dose administered for two IB courses and two CI courses. Gastrointestinal toxicities, nausea, vomiting, and diarrhea were a maximum of Grade 2 (Southwest Oncology Group criteria) and similar for both patient groups. Neuropathy was limited to paresthesias only, even after a cumulative dose of $450$ mg/m$^2$ in two CI patients. No patient required diuretics for fluid overload. Acute renal tubular toxicity was assessed by measurements of urinary AAP, NAG, and total protein. As shown in Fig. 3, the pattern of urinary enzyme and total protein excretion was qualitatively similar for the IB and CI groups. While enzyme excretion peaked on Day 6, total protein peaked between Days 6 and 9. The increases in enzyme and total protein excretion, when averaged over the 14-day period of observation, did not differ significantly between the two treatment groups. The average
The upper limits of the reference range for AAP and NAG are 3.0 and 1.1U/mmol (wliil line) and 12 courses administered by continuous infusion (dashed line).

**Three of 11 courses.**

![Graph of AAP, NAG, and Total Protein concentrations](image)

Table 2 Pharmacokinetic parameters of intermittent bolus administration

<table>
<thead>
<tr>
<th>Days</th>
<th>Maximum [Pt]_{bolus}</th>
<th>Maximum [Pt]_{interm}</th>
<th>[Pt]_{interm} exposure</th>
<th>Half-life [Pt]_{interm}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 1</td>
<td>1.6 ± 0.5* mg/liter</td>
<td>(1.1-2.6)</td>
<td>0.87 ± 0.19 mg/liter</td>
<td>(0.58-1.14)</td>
</tr>
<tr>
<td>Day 3</td>
<td>2.0 ± 0.5 mg/liter</td>
<td>(1.1-2.5)</td>
<td>0.77 ± 0.18 mg/liter</td>
<td>(0.50-0.99)</td>
</tr>
<tr>
<td>Day 5</td>
<td>2.6 ± 0.4* mg/liter</td>
<td>(1.8-3.0)</td>
<td>0.90 ± 0.19 mg/liter</td>
<td>(0.62-1.15)</td>
</tr>
</tbody>
</table>

* Mean ± standard deviation. Numbers in parentheses, range.

**Significant t test result, Day 3 versus Day 5, P = 0.02.

Table 3 Toxicity

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Continuous infusion</th>
<th>Intermittent bolus</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>No. of patients</td>
<td></td>
</tr>
<tr>
<td>Myelosuppression</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nadir WBC (cells/µl)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2,000</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>1,000</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>&lt;1,000</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Nadir platelets (cells/µl)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>50,000</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>&lt;50,000</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td></td>
<td></td>
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<tr>
<td>Hypomagnesemia</td>
<td></td>
<td></td>
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<tr>
<td>Paresthesias</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High frequency hearing loss</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Ten of 15 courses.

Our results show pharmacokinetic differences which are dependent on the method of administration of the identical dose of cisplatin. Filterable platinum exposure (AUC) was 1.5 to 2-fold greater and the half-life nearly four times longer with 5-day CI compared to a 5-day IB schedule. All differences were highly significant, P < 0.01. These differences were not a result of significant intercycle variability in a small number of patients. There were no statistically significant differences for intercycle data for AUC, half-life, and concentration parameters with either IB or CI groups. To our knowledge this is the first trial to directly compare the pharmacokinetics of continuous infusion with a high dose intermittent bolus schedule.

In the 1970s, initial Phase I clinical trials were conducted using IB dosing. DeConti et al. reported a bieponential elimination for bolus doses with an initial filterable platinum half-life of 25-49 min and a secondary phase of 58-73 h. Ninety % of platinum was protein bound within 4 h. Urine excretion was incomplete, 27-45% in the first days (18). Our data and other recent studies evaluating the pharmacokinetics of bolus and brief infusions of less than 1 h duration are in agreement with these results (19, 20-22).

In our pharmacokinetic trial, toxicity from CI and IB cisplatin was similar with the exception of myelosuppression and magnesium wasting. Thrombocytopenia and/or leukopenia occurred in all six CI patients but in only two of five IB patients.

**DISCUSSION**

Interest in the administration of cisplatin by prolonged infusion in order to improve the therapeutic index stemmed from the work of Derwinko et al. (8). Using cultured human lymphoma cells, these investigators showed that low dose continuous exposure to cisplatin resulted in cell kill equivalent to short term high dose exposure. This concept was tested in several Phase I and II clinical trials evaluating the toxicity of 24-120-h continuous infusion cisplatin (23-26). Jacobs et al. administered 50-130 mg/m² (average, 80 mg/m²) over 24 h to 18 patients with advanced head and neck cancer and concluded that the response rate was equivalent to larger bolus doses while toxicity was greatly reduced (24). Three other investigators evaluated 5-day continuous infusions ranging from 20-40 mg/m²/day (23, 25, 26). They observed a change in the toxicity profile, myelosuppression being the primary toxicity, while nephrotoxicity and gastrointestinal toxicities were mild. Lokich (23) and Posner (26) found 25-30 mg/m²/day to be the maximum tolerable dose.

In our pharmacokinetic trial, toxicity from CI and IB cisplatin was similar with the exception of myelosuppression and magnesium wasting. Thrombocytopenia and/or leukopenia occurred in all six CI patients but in only two of five IB patients.

CISPLATIN PHARMACOKINETICS

**Table 2 Pharmacokinetic parameters of intermittent bolus administration**

**Fig. 3.** Daily median concentrations of urinary AAP, NAG, and total protein during and after 10 courses of cisplatin (Days 1–5) administered by i.v. bolus (solid line) and 12 courses administered by continuous infusion (dashed line). The upper limits of the reference range for AAP and NAG are 3.0 and 1.1 U/mmol creatinine, and for total protein, 0.15 g/g creatinine.
(P = 0.06). Prolonged marrow suppression was also responsible for treatment delays occurring only in CI patients. This toxicity pattern suggests that myelotoxicity is dependent on exposure rather than peak plasma levels.

Monoeponential pharmacokinetics of prolonged cisplatin infusions (greater than 20 h) have been observed by several investigators (19, 21, 27). However, direct comparisons of 5-day CI and IB filterable platinum exposures analyzed by the same laboratory have not been reported. Filterable platinum contains unbound platinum and platinum which is bound to low molecular weight nucleophiles (sulfhydryl-containing molecules) such as amino acids or small peptide chains. The therapeutic activity of the latter is unknown. The increased exposure to filterable platinum that we observed with CI may be explained by two factors. The plasma concentration of filterable platinum increases over the duration of the 120-h constant infusion (Fig. 1) due to the continual release of protein bound platinum from tissues into the plasma compartment and its slow elimination. The elimination half-life of the cisplatin complex after termination of the infusion is similar to the rate of elimination of platinum from tissues. In addition, changes in renal reabsorption of filterable platinum may contribute to the exposure difference observed between IB and CI cisplatin. Renal clearance of platinum involves tubular secretion and reabsorption (28). Reece (29) has shown that in patients receiving bolus cisplatin, tubular reabsorption is saturated immediately after drug is infused, when plasma and urinary platinum levels are high. As these levels decline, proportionally more reabsorption occurs with a reduction in renal clearance. Thus CI of cisplatin may avoid saturation of this transport leading to increased reabsorption of potentially active platinum species and prolonged plasma levels of filterable platinum.

In contrast, a biphasic decrease in filterable platinum occurs after IB cisplatin. The initial rapid elimination phase has a half-life of approximately 30 min and is due to the elimination of the cisplatin coordination complex or the active, nonprotein-bound platinum. The second much longer phase is due to the turnover of protein-bound platinum from tissues. When only a single-kinetic elimination term was used in the data evaluation, the half-lives for filterable platinum eliminations were significantly longer for the CI schedule. Our observations are consistent with pharmacokinetic models established by Farris et al. (30).

Our increase in AUC with CI stands in contrast to that of Vermorken et al. (31), who reported similar AUCs for 100 mg/m² dosages as 8-min, 3-h, and 24-h infusions. This literature data was for only one course of therapy with each infusion protocol as compared to multiple patients and courses with our study. Moreover, the dose-rate (mg/h) for CI in our study was substantially lower than that reported by Vermorken. The observed increase in AUC with extended infusions has been previously reported (21).

In summary, we found that a total dose of 150 mg/m² of cisplatin administered in divided dose over 5 days by CI or IB was tolerable. Gastrointestinal toxicity, ototoxicity, and neuropathy were mild and not treatment limiting. The exposure to filterable platinum was significantly increased by CI. Although the actual amount of free platinum or active drug is unknown, a therapeutic advantage may result from a continuous infusion of cisplatin. The spectrum of toxicity appears different with CI as suggested by the increase in myelosuppression in this series of patients. One may speculate that there is a continuum between the nephrotoxicity associated with maximum peak plasma levels and the nonrenal toxicities of maximum-filterable platinum exposure. Based on the increase in AUC, our results suggest that single agent cisplatin in a dose of 150 mg/m² administered as a 5-day CI may approach an optimal therapeutic index producing acceptable toxicity. The response rate of this regimen remains to be defined in larger numbers of patients. However, results of Phase II trials suggest that bolus cisplatin in doses of up to 200 mg/m² produce higher response rates than conventional doses of 80–120 mg/m² (4, 6, 9) although cumulative toxicities limit treatment. While various hydration schemes have been developed to minimize the risk of nephrotoxicity, in our experience, the daily administration of low total doses, either by bolus or continuous infusion does not require excessive hydration, forced diuresis, and multidrug prophylactic antiemetic regimens. Our results provide a pharmacokinetic rationale for further testing of CI cisplatin in larger numbers of patients to determine if a therapeutic advantage does exist.

ACKNOWLEDGMENTS

The following students at Providence College assisted in the platinum analyses: Paula Joly and Eric Ingersoll. The authors thank Hank Griffin and the personnel at the Chemistry and Materials Laboratories at Texas Instruments, Inc., Attleboro, MA, for granting permission to use their two plasma emission spectrometers and for their invaluable technical assistance. We acknowledge Barbara Blair for technical assistance with the renal enzyme studies. We wish to thank Wilma Savitski for expert secretarial assistance.

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