[CANCER RESEARCH 48, 4423–4426, August 1, 1988]

# Acodazole Hydrochloride: Phase I Trial, Pharmacokinetics, and Evaluation of Cardiotoxicity in Dogs[1]

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## ABSTRACT

**Acodazole (NSC 305884) was examined in a Phase I trial evaluating a 1-h infusion repeated every 21 days in 37 patients with advanced carcinomas. Cardiac toxicity was dose-limiting at 1370 mg/m², manifested as multiple premature ventricular contractions, $QT_c$ interval prolongation, and decreasing heart rate. Other toxicities included mild to moderate nausea and vomiting and local reaction near the i.v. injection site requiring the use of central venous catheters. Antineoplastic activity was not observed. Acodazole levels assayed by high-performance liquid chromatography disclosed a peak plasma level of 19 ± 4 (SEM) μg/ml for 1370 mg/m². Acodazole plasma levels decreased in a triphasic manner over a 100-fold range. The volume of distribution at steady state was 238 ± 18 liter/m² suggesting extensive tissue binding. The total body clearance was 13.6 ± 0.9 liter/h/m²; the percentage of urinary excretion was 29 ± 2% for 48 h. To evaluate cardiac toxicity, acodazole was administered to five dogs at 2262 mg/m² (1-h infusion) which provided plasma concentrations similar to those achieved at 1370 mg/m² in humans. Consistent findings in dogs were drug-related prolongation of $QT_c$ intervals, and reduction in heart rate, left ventricular *dP/dt*, and mean blood pressures. Clinical development of acodazole requires studies to further elucidate and alleviate this cardiac toxicity.**

## INTRODUCTION

Acodazole hydrochloride (NSC 305884) is a water-soluble imadazoquinoline derivative originally synthesized by Snyder *et al.* (1). Structural features and *in vitro* studies suggest that acodazole may function as a DNA-intercalating agent (2, 3).

The antineoplastic activity of acodazole was observed in the i.p.-implanted murine B16 melanoma (49–98% ILS[3]), the i.p. P388 leukemia (58–81% ILS), and the i.p. L1210 leukemia (<50% ILS) models. Acodazole was inactive in the $CD8F_1$ mammary tumor, colon 38, and the Lewis lung murine carcinomas. Inactivity was also observed in the human xenografts, including lung (LX-1), colon (CX-1), and mammary (MX-1) tumors (2).

Preclinical toxicology studies in mice and dogs suggested central nervous system toxicity after rapid administration of acodazole. Toxicity to the hematopoietic, gastrointestinal, and hepatic systems were noted (2).

A Phase I evaluation of acodazole administered as a 1-h i.v. infusion every 21 days is reported below. The aims were to determine the clinical toxicities, maximum tolerated dose, pharmacokinetics, and antineoplastic activity. To further characterize the cardiac toxicity observed in patients, acodazole was evaluated in a dog model.

## MATERIALS AND METHODS

**Study Design.** This study was designed as a Phase I trial starting at "N" and escalating the dose according to the modified Fibonacci method. The study was initiated at a dose of 25 mg/m² (1/10 of the murine lethal dose for 10% of animals) administered initially as a 15-min i.v. infusion every 21 days. Although the infusion time was originally 15 min, the administration time was extended to 1 h because of hypotension observed in other Phase I studies. Planned excalations were 50, 100, 150, 225, 280, 360, 450, 560, 700, 875, 1095, and 1370 mg/m². Although registration began at 25 mg/m², subsequent patients were entered at 280 mg/m² since toxicities were not observed between 50–225 mg/m² in concurrent studies. At least three patients were entered at each level and followed for 20 days prior to dose escalation. Patients completing two nontoxic courses at a dose level could be escalated to a higher level if three previously untreated patients were entered.

**Patient Selection.** After informed consent was obtained, patients with histologically proven advanced carcinomas were entered on the study. All patients were required to have recovered from acute toxicities of prior therapy. Adequate marrow reserve (WBC count >4000 mm³ and platelet count >100,000/mm³), serum creatinine <2.0 mg/dl, and total bilirubin <2.0 mg/dl were required. Patients with a history of acute myocardial infarction, congestive heart failure, clinically significant arrhythmias, or uncontrolled seizures were ineligible.

**Drug Preparation and Administration.** Acodazole was supplied by the National Cancer Institute, Division of Cancer Treatment (Bethesda, MD), in 200-mg vials prepared as a light yellow lyophilized powder with 120 mg of mannitol. When reconstituted with 3.6 ml of 0.9% sodium chloride solution each ml contains 50 mg acodazole and 30 mg of mannitol (2). The required amount of drug was further diluted in 0.9% sodium chloride solution to a final concentration of 4 mg/ml and was administered over 1 h in the antecubital vein or central venous line using an IVAC pump (IVAC Corporation, San Diego, CA).

**Treatment Evaluation.** Pretreatment evaluation included a complete history and physical examination, lesion measurements, complete blood counts, urinalysis, multichannel chemistries (to include serum creatinine, bilirubin, calcium, uric acid, serum glutamic-oxaloacetic transaminase, lactic dehydrogenase, and alkaline phosphatase), electrocardiogram, and chest X-ray. These studies were repeated every 4 weeks or at the time of off-study. Physical examinations, complete blood counts, and multichannel chemistries were performed weekly. Blood pressure and pulse were recorded every 15 min during the acodazole infusion.

**Response Criteria.** Maximum tolerated dose was defined as that dose which produced predictable and reversible toxicity but did not incapacitate or interfere with the patient's well being or general function. Complete response required complete disappearance of all evidence of disease. A partial response was defined as a 50% or greater decrease in the sum of the products of the two greatest dimensions of measurable lesions accompanied by stabilization or improvement in performance status for at least 1 month. Stable disease was defined as a decrease in tumor size less than 50%; progressive disease was defined as an increase in the size of measurable lesions or the appearance of new lesions (4).

**Acodazole HPLC Assay in Biological Samples.** Heparinized blood samples (2 ml) were collected at predose, 30, and 60 min during the

Received 12/3/87; revised 4/5/88; accepted 4/26/88.

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[1] This study was supported in part by Phase I Contract N01-CM-27551 of the National Cancer Institute, Bethesda, MD, and by the Ben Kasle Trust Fund for Cancer Research, Detroit, MI.

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[3] The abbreviations used are: ILS, increase in lifespan; AUC, area under the curve; HPLC, high-performance liquid chromatography; LV *dP/dt*, rate of left ventricular pressure change; LVEDP, left ventricular end-diastolic pressure; LVP, left ventricular pressure; PVC, premature ventricular contraction; $QT_c$, QT interval corrected for heart rate; *V*, volume of distribution.

infusion; 10, 20, 30, 40, 50, and 60 min and 2, 3, 4, 5, 6, 12, 18, 24, 36, and 48 h postinfusion. Blood samples were centrifuged at 1200 × *g* for 15 min and the plasma was frozen at −20°C until analysis. Total urine volumes were recorded and an aliquot of 20 ml was frozen from each collection period. Acodazole levels in biological fluids were assayed by HPLC, using a method developed by Dr. L. Malspeis, Ohio State University, School of Pharmacy (Columbus, OH). This method uses an Amberlite XAD-2 precolumn (2 x 50 mm) for sample clean-up and enrichment placed before the analytical column (Ultrasphere-Cyano, 5 μm, 4.6 x 150 mm). The biological samples (or dilutions) were injected (100 μl) onto the precolumn which is then washed for 3 min with an aqueous buffer (0.01 M, potassium phosphate, pH 8.5, 1 ml/min). The drug is concentrated at the top of the XAD-2 column. With a switching valve in the "back-flush" mode, acodazole is displaced from the precolumn to the analytical column using a mobile phase of 0.1 M ammonium formate:acetonitrile (60:40), pH 5.5, at a flow of 1.5 ml/min. The UV detector (Spectroflow 773; Kratos Analytical) was set at 345 nm. The retention time of acodazole was 6 min. Calibration curves were linear within 0 to 1000 ng/ml with correlation coefficients near unity. The lowest detectable concentration was 25 ng/ml.

**Pharmacokinetic Analysis.** Postinfusion drug levels *versus* time data were best fitted to a three-compartment open model with elimination from a central compartment connected with a shallow and a deep peripheral compartment. The equation describing this model is

$$C = A_1e^{-\alpha t} + A_2e^{-\beta t} + A_3e^{-\gamma t}$$

After curve stripping by the method of residuals, the data were fitted to the model by nonlinear regression (PCNONLIN; Statistical Consultants, Lexington, KY) with a data weight of $1/C^2$. The AUC was calculated by the trapezoidal method from time zero to infinity, including the infusion time. For the calculation of $V_c$ (dose/$C_o$; the volume of the central compartment), the coefficients obtained after the infusion were related to their corresponding i.v. bolus coefficients for the calculation of $C_o$ (the concentration at time 0). The other pharmacokinetics parameters were calculated as described by Gibaldi and Perrier (5).

**Dog Model to Evaluate Cardiac Toxicity.** Five mongrel dogs of either sex, weighing between 15 and 22 kg, were anesthetized with sodium pentobarbital (30 mg/kg i.v.), intubated and ventilated with room air using a Harvard respirator. Cannulas were positioned in the left carotid artery for the measurement of arterial blood pressure. Cannulas were also placed in the left jugular vein for the infusion of fluids, drugs, and withdrawal of blood samples. A left thoracotomy was performed at the fifth intercostal space and a pericardial cradle was temporarily constructed. Via the left atrium, a micromanometer-tipped catheter (Millar Instruments, Houston, TX) was positioned in the left ventricle for the measurement of LVP, LVEDP, and LV *dP/dt*. Electrodes were placed in each limb to monitor standard limb electrocardiograms.

After baseline hemodynamic recordings on a Gould multichannel recorder and blank venous blood samples were obtained, acodazole (60 mg/kg) was infused i.v. for 1 h. This acodazole dose was determined by multiplying a conversion factor of 1.87 to the highest dose administered to humans (1370 mg/m²). Hemodynamics and venous blood samples were collected every 15 min for 2 h, and then hourly until 4 h. At 3 h postinfusion the dogs were euthanized with sodium pentobarbital and tissue samples from heart, liver, kidney, and striated muscle were collected, washed in cold saline, and frozen until analysis. The tissues were homogenized in saline using a Polytron homogenizer and an aliquot of the homogenate (or a dilution) was injected on the HPLC as described above. The calibration curves were run in the same tissues under study.

## RESULTS

**Patient Characteristics and Accrual.** Thirty-seven patients were entered on this Phase I study. Patient characteristics are presented in Table 1.

**Toxicities.** No hematological toxicity was observed at any dose level. Gastrointestinal toxicity, manifested as mild to moderate nausea and vomiting, was observed consistently at each level and responded to conventional antiemetics (*e.g.*, prochlorperazine). Prophylactic antiemetics were not administered.

Table 1 *Patient characteristics*

| | |
|---|---|
| No. of patients entered | 37 |
| Male/female | 17/20 |
| Median age | 59 |
| Median performance status | 70 |
| Previous therapy | |
| Chemotherapy | 34 |
| Radiation therapy | 26 |
| Surgery | 27 |
| Disease category | |
| Bronchogenic carcinoma | 9 |
| Soft tissue sarcoma | 4 |
| Gastrointestinal carcinoma | 12 |
| Genitourinary carcinoma | 4 |
| Breast carcinoma | 8 |

Table 2 *Changes in serum cations, $QT_c$ intervals, and drug levels in a patient receiving 1370 mg/m² of acodazole*

| Time (min) | K (meq/liter) | Mg (meq/liter) | Ca (mg/dl) | $QT_c$ (ms) | Drug level (μg/ml) |
|---|---|---|---|---|---|
| 0 | 3.2 | 1.7 | 8.7 | 0.43 | 0 |
| 45 | 3.0 | 1.6 | 8.6 | 0.52 | 23.3 |
| 75 | 2.6 | 1.4 | 7.7 | 0.6 | 7.62 |
| 105 | 2.7 | 1.4 | 7.5 | 0.5 | 5.4 |
| 300 | 3.2 | 1.4 | 8.0 | 0.54 | 2.85 |

Local reactions to acodazole included redness and edema near the antecubital venous injection site at 25–280 mg/m² levels. This reaction was not related to drug extravasation. Pain at the injection site was also experienced by patients at 360 mg/m² level. Consequently, acodazole was injected via a central venous catheter in subsequent patients.

Four patients developed allergic reactions to acodazole. Three patients (1095 and 1370-mg/m² levels) developed hives and urticarial reactions which responded to oral antihistamines and corticosteroids. The most serious reaction was observed in a patient receiving 875 mg/m² who developed anaphylactic shock, requiring intubation and administration of epinephrine, corticosteroids, and antihistamines. This toxicity completely resolved, but required intensive care unit support for 24 h.

Cardiac toxicity became dose limiting at 1370 mg/m². Two patients without cardiac histories and with normal electrocardiograms, developed PVCs during infusion of acodazole. PVCs were unifocal, appearing at the end of the infusion, and resolved within 90-min postinfusion. This abnormality was not detected on subsequent electrocardiographic follow-up. Since the QT interval may increase with a decreasing heart rate, $QT_c$ intervals were determined. The $QT_c$ is the QT interval corrected for heart rate. In one patient the $QT_c$ increased from 0.43 ms (pretreatment) to a maximum value of 0.60 ms (15-min postinfusion). The heart rate decreased from 85 to 60 bpm. As the $QT_c$ increased, a decrease in serum potassium, magnesium, and calcium levels were noted in the last patient treated (Table 2). These decreases in serum cations were observed 15–30 min postinfusion. We were unable to document similar cation decreases in other patients. Due to cardiac toxicity and decreases in serum cations, patient entry was curtailed.

**Response.** Partial or complete responses were not observed in this Phase I study.

**Pharmacokinetic Data.** The plasma concentration *versus* time curves showed a triphasic decay over 2 logs (Fig. 1). The mean peak concentrations at the completion of the infusion ranged from 9.8 to 19.2 μg/ml from the lowest dose (360 mg/m²) to the highest dose (1370 mg/m²) (Table 3). The mean AUC ranged from 34.5 to 85.8 μg/ml/h for the 360 and 1370 mg/

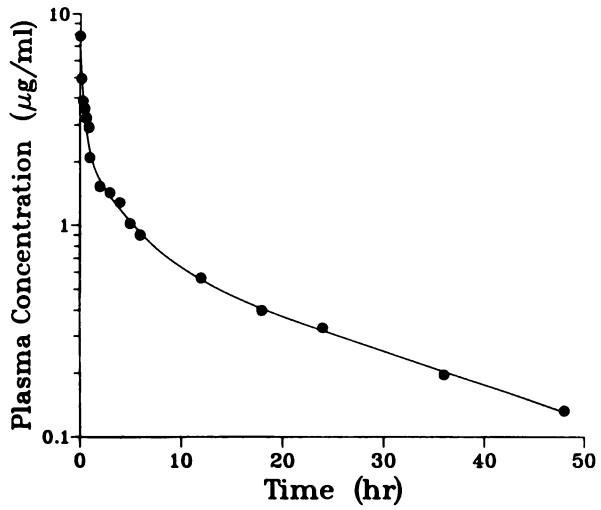


Fig. 1. Representative acodazole plasma concentration *versus* time curve. This patient received 360 mg/m² of acodazole as a 1-h infusion. ●, acodazole concentration; ——, nonlinear regression analysis.

m² dose, respectively. No significant change in half-life, volume of distribution, clearance, or urinary excretion were observed as a function of dose. Mean half-lives were 0.14, 2.5, and 19.5 h, for the $\alpha$, $\beta$, and $\gamma$ phases, respectively. Volumes of distribution were 16.7 liters/m² for the central compartment ($V_c$), 370 liters/m² for the $\gamma$ phase ($V_\gamma$), and 238 liters/m² for the steady state ($V_{ss}$). Total body clearance was 13.6 liters/h/m². The 48-h urinary excretion of unchanged acodazole was 29%.

**Cardiac Toxicity in the Dog Model.** To further investigate the cardiac toxicity, acodazole was administered as a 1-h i.v. infusion to five dogs at a dose (2262 mg/m²) equivalent to the maximum tolerated dose in this Phase I trial (1370 mg/m²). Plasma concentrations of a patient who experienced cardiac toxicity of this dose level are presented in Fig. 2*A* along with similar plasma levels reproduced in the dog model (Fig. 2*B*). In addition to acodazole plasma levels, hemodynamics, electrocardiogram, electrolytes, creatinine, magnesium, ionized calcium, phosphorus, and tissue acodazole levels were monitored. Urinary electrolytes, magnesium, ionized calcium, and creatinine were also analyzed.

A reduction in preinfusion compared to immediate postinfusion values were observed for heart rate (133 ± 13 to 99 ± 18 beats/min, $P < 0.01$), mean arterial blood pressure (113 ± 6 to 66 ± 8 mm Hg, $P < 0.01$), and left ventricular systolic pressure (123 ± 5 to 86 ± 8 mm Hg, $P < 0.01$). LVEDP remained unchanged. Acodazole prolonged the $QT_c$ intervals from 319 ± 22 to 348 ± 17 ms ($P < 0.05$) but did not affect significantly the PR or QRS intervals. Administration of acodazole to dogs did not alter urinary or plasma cations.

Acodazole levels measured in tissues were higher than simultaneous plasma concentrations at 3-h postinfusion. Acodazole levels in myocardium, liver, kidney, and striated muscle were 171 ± 34, 326 ± 24, 365 ± 24, and 21 ± 5 μg/g of wet tissue, respectively. Compared to the simultaneous plasma concentrations (3.2 μg/ml), acodazole levels were 53-fold higher in myocardium, 102-fold higher in liver, 114-fold higher in kidney, and 6.6-fold higher in striated muscle.

## DISCUSSION

Acodazole was examined in a Phase I study using a 1-h infusion repeated every 21 days in 37 patients with advanced carcinomas. Although cardiac toxicity was not recognized during preclinical evaluation, this dose-limiting toxicity was observed in our Phase I trial and could be reproduced in the dog model.

Clinical cardiac toxicity manifested as PVCs were noted at the 1370 mg/m² level. Electrocardiograms revealed bradycardia and prolongation of $QT_c$ intervals. The QT interval represents ventricular repolarization, a phase when the myocardium is susceptible to ventricular arrhythmias. Although a recognized association exists between $QT_c$ prolongation and arrthymias, no clear relationship exists between the extent of $QT_c$ prolongation and risk of ventricular arrhythmias (6). Patients did not receive medications known to prolong $QT_c$ (*e.g.*, quinidine, procainamide, diisopyramide, phenothiazines). The PR and QRS intervals were unaffected in our patients.

Cardiac toxicity was also observed in a Phase I study of acodazole at the University of Wisconsin (7). Using a weekly × 4 schedule, these investigators reported prolongation of QT intervals with polymorphic ventricular tachycardia ("torsades de pointes") at the 1184 mg/m² level. Using a modified weekly schedule of 340–888 mg/m², prolongation of the $QT_c$ was noted at all dose levels. No relationship was demonstrated between acodazole dose and the occurrence or degree of $QT_c$ prolongation. Alterations in blood pressure, occurrence of ventricular arrhythmias, or reduction in serum cations were not observed between 340 and 888 mg/m².

Our dog studies indicate that acodazole induces severe bradycardia, hypotension, and reduces the contractile state of the myocardium at similar plasma concentrations as in our clinical study. Acodazole induced moderate prolongation of the $QT_c$ in dogs. The duration of the PR and QRS intervals remained unchanged. Acodazole concentrations in the myocardium (53-fold greater than simultaneous plasma levels) indicate a high affinity of the drug for the myocardium, especially in comparison to striated muscle.

Table 3 *Acodazole pharmacokinetics in patients*

Patients received acodazole as a 1-h i.v. infusion

| Dose (mg/m²) | N | $C_p$[a] (μg/ml) | Half-lives (h) | | | AUC[b] (μg/ml/h) | Volumes (liters/m²) | | | $Cl_{TB}$ (liter/h/m²) | % of urinary excretion[c] |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | α | β | γ | | $V_c$ | $V_\gamma$ | $V_{ss}$ | | |
| 360 | 4 | 9.8 ± 1.2[d] | 0.16 ± 0.04 | 2.5 ± 0.6 | 18.3 ± 7.2 | 34.5 ± 4.0 | 11.5 ± 4.3 | 366 ± 65 | 207 ± 34 | 10.8 ± 1.2 | 29 ± 8 |
| 450 | 3 | 10.0 ± 1.6 | 0.17 ± 0.07 | 1.3 ± 0.5 | 14.1 ± 3.7 | 44.6 ± 6.8 | 13.2 ± 3.9 | 200 ± 22 | 146 ± 15 | 10.6 ± 1.4 | 25 ± 3 |
| 700 | 5 | 10.3 ± 2.6 | 0.13 ± 0.04 | 2.1 ± 0.3 | 14.7 ± 2.3 | 48.6 ± 6.2 | 19.7 ± 5.5 | 315 ± 54 | 222 ± 40 | 15.3 ± 1.9 | 25 ± 2 |
| 875 | 3 | 17.4 ± 2.8 | 0.16 ± 0.03 | 3.1 ± 0.4 | 26.2 ± 0.2 | 71.0 ± 18.3 | 17.9 ± 6.0 | 483 ± 159 | 264 ± 35 | 12.7 ± 4.1 | 27 ± 3 |
| 1095 | 3 | 15.1 ± 3.1 | 0.10 ± 0.03 | 4.6 ± 1.1 | 19.9 ± 1.6 | 75.0 ± 15.7 | 18.8 ± 7.7 | 445 ± 64 | 261 ± 37 | 15.8 ± 3.0 | 36 ± 8 |
| 1370 | 3 | 19.2 ± 4.1 | 0.14 ± 0.02 | 1.9 ± 0.4 | 19.6 ± 3.4 | 85.8 ± 6.5 | 18.6 ± 5.1 | 445 ± 44 | 351 ± 14 | 16.2 ± 1.2 | 32 ± 11 |
| Mean ± SEM | | | 0.14 ± 0.02 | 2.5 ± 0.3 | 19.5 ± 1.5 | | 16.7 ± 2.1 | 370 ± 34 | 238 ± 18 | 13.6 ± 0.9 | 29 ± 2 |

[a] Plateau concentration at the end of infusion.
[b] AUC total from the beginning of infusion to infinity.
[c] Percentage of urinary excretion in 48 h.
[d] Mean ± SEM.

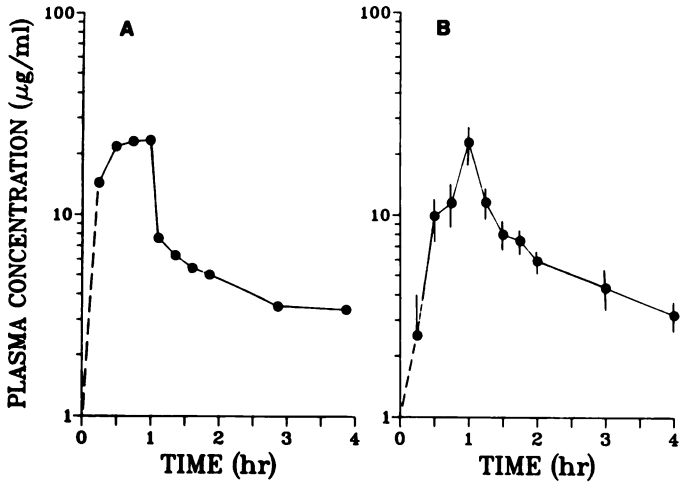


Fig. 2. Acodazole plasma concentrations in a patient who experienced cardiac problems (PVCs) near the completion of the infusion at the dose level of 1370 mg/m$^2$ (*A*). Acodazole plasma concentrations in dogs ($N = 5$) who received 2562 mg/m$^2$ as a 1-h infusion (*B*).

The etiology of the prolongation of $QT_c$ and the development of ventricular arrhythmias is complicated by the drop in serum potassium, magnesium, and calcium observed in our last patient. Hypokalemia and hypomagnesemia may increase the QT interval. Although we were able to document electrocardiographic changes of $QT_c$ prolongation and ventricular arrhythmias in dogs similar to our clinical study, we were unable to demonstrate any changes in the serum and/or urinary cations. Investigators at the University of Wisconsin measured serum magnesium, calcium, and potassium and were unable to document any changes between pre- and postinfusion values (7). Although alterations in cations were observed in the last patient treated as outlined in Table 2, both our animal study and the University of Wisconsin report fail to implicate these changes in the prolongation of $QT_c$ with acodazole.

Nausea and vomiting were consistently observed and treated with conventional antiemetics. Moderate nausea and vomiting were also reported in the University of Wisconsin study at doses greater than 225 mg/m$^2$. Acodazole produced systemic allergic reactions in four patients and one patient experienced anaphylactic shock at the 875-mg/m$^2$ level. Patients receiving acodazole should be closely observed for the possible development of systemic allergic reactions. Local reactions manifested as redness and edema at injection site have been noted. These "flare reactions," previously described for doxorubicin, are unrelated to drug extravasation (8). Reversible inflammation and swelling near the area of the infusion have been previously reported (7, 9). Local tissue reactions were circumvented by insertion of central venous catheters in our patients. Although not observed in our 1-h infusion, other toxicities have included renal toxicity, hypotension, and painful paresthesias when acodazole was administered as a 10- to 20-min i.v. infusion (8).

Acodazole pharmacokinetics in patients revealed a triphasic decay with a prolonged terminal half-life. Volumes of distribution of the terminal phase and steady state were large, suggesting extensive tissue binding. In addition, high tissue concentrations in dogs corroborate the extensive tissue binding of acodazole. Other pharmacokinetic parameters were similar to those reported in concurrent Phase I studies (7, 10).

Cardiac toxicity was dose limiting in this Phase I study of acodazole administered as a 1-h infusion repeated every 21 days. This toxicity was recognized at 1370 mg/m$^2$ by a reduction in heart rate and prolongation in $QT_c$ intervals with subsequent development of PVCs. Prolongation of the $QT_c$ has been reported between 340 and 888 mg/m$^2$ and a clearly defined dose-response relationship to this toxicity could not be demonstrated (7). The relationship between dose, prolongation of $QT_c$, and the development of potentially life-threatening arrhythmias remains unclear. Therefore, we cannot recommend a Phase II starting dose. Clinical development of acodazole requires studies to further elucidate and alleviate this toxicity.

## ACKNOWLEDGMENTS

We thank the 4-Center Harper Hospital nursing personnel for their excellent collaboration during this study and Mary Phillips for data management of the clinical Phase I study. We also thank Susan Marier and Kathleen Rutkowski for laboratory assistance, and Daniel Beaulieu, PA-C, and Elizabeth O'Connor, PA-C, for their clinical assistance.

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