Phase 1 Trial and Assay of Rubidazone (NSC 164011) in Patients with Advanced Solid Tumors

John S. Kovach, Matthew M. Ames, Margo L. Sternad, and Michael J. O'Connell

Abstract

A new high-pressure liquid chromatographic method was developed for the simultaneous determination of rubidazone and daunorubicin in human plasma at concentrations as low as 60 ng/ml. Clinical toxicity and the stability of rubidazone were studied in nine patients with advanced solid tumors. Rubidazone was administered by i.v. infusion over 1 hr on a single day every 4 weeks. Moderate leukopenia was the dose-limiting toxicity in four of six patients treated at 150 mg sq/m. Assay of rubidazone in plasma samples obtained after administration of rubidazone showed that the drug was stable for at least 7 hr.

Introduction

Rubidazone (NSC 164011), an investigational anthracycline antibiotic, is the benzoylhydrazone derivative of daunorubicin (Chart 1). Rubidazone has antitumor activity against L1210 and Bi6 animal tumor systems (8). Like daunorubicin and Adriamycin, it is more effective against L1210 leukemia. None of these drugs shows schedule dependency in these systems (8).

Rubidazone has been studied primarily in patients with acute leukemia (3, 5, 11). Jacquillat (11) reported a complete remission rate of 50% in 44 patients with acute lymphocytic leukemia and a rate 57% in 70 patients with previously untreated acute myelocytic leukemia. Recently, Benjamin et al. (3) reported a complete response rate of 33% (13 of 39) in adults with acute leukemia. A single dose of 450 mg/sq m was felt to produce optimal therapeutic effect (3). In patients with previously treated acute leukemia, the major toxic effects of rubidazone were thrombocytopenia and granulocytopenia (3). Maintenance doses of 200 mg/sq m resulted in severe granulocytopenia (median, 420/µl) and moderate thrombocytopenia (median, 67,000/µl). Fatal cardiomyopathy following cumulative doses of rubidazone of 1700 to 2600 mg/sq m occurred in 3 patients previously treated with 135- to 270-mg/sq m total doses of other anthracyclines (3).

The relative cardiotoxicity of rubidazone compared to other anthracyclines in humans remains to be determined. Of particular interest is a report by Zbinden and Brandle (10) that rubidazone given at the plasma concentrations achieved following administration of rubidazone at doses up to 200 mg/sq m by 1-hr infusion. A new HPLC method was developed for the simultaneous assay of rubidazone, daunorubicin, and daunorubicinol in human plasma.

This Phase 1 study was designed to determine the clinically tolerable dosage of rubidazone given as a single dose in patients with advanced solid tumors with no evidence of impaired hematopoiesis and to determine the stability of rubidazone in vitro and in vivo.

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1 Supported in part by National Cancer Institute Contract CA 15083 and National Cancer Institute Grant CA 15083 FF.
2 To whom requests for reprints should be addressed.
3 D. M. Young, unpublished data.
4 Rhone-Poulenc, Paris, personal communication.
5 The abbreviations used are: HPLC, high-pressure liquid chromatography; TLC, thin-layer chromatography.
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Chart 1. Structures of rubidazone, daunorubicin, and daunorubicinol.

MATERIALS AND METHODS

Patients. All patients had histologically proven advanced carcinoma beyond hope of surgical cure. None had major surgical procedures, chemotherapy, or radiation therapy within the 4 weeks prior to study. Patients with severe malnutrition, persistent vomiting, recurrent gastrointestinal bleeding, azotemia (serum creatinine, >1.5%), or any elevation of direct-reacting serum bilirubin were excluded. All patients were ambulatory and received therapy on an outpatient basis. None had received prior treatment with an anthracycline, and none had evidence of active heart disease as defined by myocardial infarction in the 3 months prior to treatment, heart block, congestive heart failure, or angina pectoris. No patient had received radiation therapy to the entire pelvis or lumbosacral spine. Pretreatment characteristics of the 9 patients studied are summarized in Table 1.

Clinical Studies. The following laboratory determinations were obtained within 3 days prior to the initiation of therapy: WBC, hemoglobin, platelet, differential blood count, urinalysis, serum chemistry profile including creatinine, serum glutamic-oxaloacetic acid transaminase, alkaline phosphatase, direct and total bilirubin, electrocardiogram, and chest X-ray. Weight, symptomatic status, and performance status were assessed on the day of initiation of therapy. All parameters as well as a complete physical examination were repeated at 4-week intervals. WBC were obtained twice weekly, and platelet counts were obtained once weekly for 3 weeks following drug administration. Rubidazone was dissolved in buffer supplied by Rhodia Corporation (50 mg of rubidazone in 4 ml of 0.2 M sodium glycinate, pH 7.0), diluted in 5% dextrose in water to a final concentration of 1 mg/ml, and infused i.v. over 1 hr. Dosages for each treatment were given in planned escalations beginning at 100 mg/sq m and repeated every 4 weeks. All patients received 25 mg of benadryl i.v. prior to each infusion. Phenothiazines were used to control nausea and vomiting if necessary.

Assay Procedures. Five ml of venous blood were removed with a plastic syringe immediately before drug administration, at intervals over an 8-hr period following drug administration, and at 24 hr in 6 patients receiving a total rubidazone dose of 150 mg/sq m. The blood was introduced immediately into a 5-ml heparin vacutainer and placed on ice. It was centrifuged at 2000 x g for 5 min, and the plasma was frozen at −70°.

The extraction procedure is a modification of the method of Finkel et al. (6) for the extraction of daunorubicin from plasma. Plasma (1 ml) was diluted with an equal volume of 0.01 N sodium hydroxide to give a final pH of 9.0. A volume of butanol equal to the volume of the diluted sample was added, and the solution was vortexed vigorously for 15 sec. The resulting gel was frozen at −70° for at least 1 hr, thawed at room temperature, and centrifuged at 10,000 x g for 10 min at 4°. The upper butanol layer was used directly for assay.

HPLC of the butanol extracts was carried out on a Partisil PX 10/25 PAC column (Whatman) with a mobile phase of chloroform:methanol:Tris-HCl, 0.2 M, pH 7.6 (92:8:0.1). This system completely resolves rubidazone, daunorubicin, and daunorubicinol.

Detection was accomplished with a Schoeffel HPLC fluorescence detector with excitation at 252 nm and an emission filter with a 520-nm cutoff. Measurement of peak areas was done with a Hewlett-Packard Model 3380A integrator. Quantitation was carried out by comparison of peak areas of extracts of unknown samples to a linear standard curve of peak areas of known concentrations of drug. As an independent check of the accuracy of measurement, daunorubicinol was used as an internal standard. For these studies, plasma samples were divided into 2 portions. To one portion, an aqueous solution of daunorubicinol was added to give a final concentration of 0.5, 1.0, or 5.0 μM, and both portions were extracted. Quantitation of rubidazone in the sample containing the internal standard was accomplished by comparing the ratio of the peak area of rubidazone to daunorubicinol in the unknown extract to a linear curve of the ratio of rubidazone to daunorubicinol in extracts of standard samples.

The plasma concentrations of rubidazone, daunorubicin, and metabolites possessing the spectral characteristics of anthracyclines (total anthracycline equivalents) were determined by measurement of fluorescence (6) of the butanol extract at 583 and 554 nm on excitation at 470 nm in an Aminco Bowman or SLM Series 8000 spectrofluorometer. Efficiency of extraction was determined by comparing the total fluorescence of butanol extracts of pooled plasma samples containing known amounts of rubidazone, daunorubicin, or daunorubicinol to the total fluorescence of known amounts of the drugs in butanol, in butanol previously exposed to normal pooled plasma adjusted to pH 9 with sodium hydroxide, and in 75% ethanol:0.45 N hydrochloric acid. Sensitivity of detection and efficiency of extraction of each drug by the butanol extraction method and by the acid:alcohol method reported by Bachur et al. (2) were compared at concentrations ranging from 10 nM to 100 μM.

Rubidazone, daunorubicin, daunorubicinol, and daunorubicinone (the aglycone of daunorubicin) were also identified in extracts of plasma and in standard solutions by TLC on nonfluorescent silica sheets or glass plates (Eastman Kodak; 100 μm) using solvent systems consisting of the lower layer of a 2-phase system formed by mixing chloroform:methanol:14.5% ammonium hydroxide or water (50:25:25). The stability of rubidazone and daunorubicin during TLC separation in both solvent systems was studied by drying the sheets in room air, scraping the separated
encountering severe hematological toxicity. The median day nadir of leukopenia was Day 14, and the median day of one patient tolerated escalation to a dose of 200 mg/sq m, were kindly provided by the National Cancer Institute, compounds from the sheet, eluting them with ethanol, and reanalyzing the eluates by TLC or by HPLC.

Samples of nonformulated rubidazone and daunorubicin were kindly provided by the National Cancer Institute, Bethesda, Md., and daunorubicinol was provided by N. R. Bachur, Baltimore, Md., and R. S. Benjamin, Houston, Texas. Daunorubicinone was prepared by a modification of the method of Arcamone et al. (1). Daunorubicin, at a concentration of 1 mg/ml in 0.1 N hydrochloric acid, was kept at 100° for 30 min. After cooling, the daunorubicinone was extracted with butanol, concentrated by evaporation under a stream of nitrogen, and purified by TLC using either of the 2 solvent systems described above.

RESULTS

Clinical Observations. The major toxicity was leukopenia. Three patients receiving rubidazone at a dose of 100 mg/sq m had no myelosuppression. A WBC nadir less than 3000 occurred in 4 of 6 patients receiving initial therapy at 150 mg/sq m and in 7 of 14 cycles at this dose. Five of 9 patients had a second course at the same dose without an increase in severity of toxicity. One patient had 4 courses at 150 mg/sq m with increased severity of leukopenia following the fourth course (nadir 980 cells/μl versus median nadir value of 3000 cells/μl for the first 3 courses). Two patients tolerated escalation to a dose of 200 mg/sq m, and one patient tolerated escalation to a dose of 200 mg/sq m, and one patient tolerated escalation to 250 mg/sq m without encountering severe hematological toxicity. The median day nadir of leukopenia was Day 14, and the median day of recovery was Day 20, with complete recovery of leukopenia occurring after Day 21 in 4 of 21 courses (Days 24, 26, 27, and 28). The median day nadir of thrombocytopenia was Day 12. In no instance was the platelet count less than 115,000 platelets/μl.

Other toxicities included mild nausea and vomiting after 7 of 21 treatment cycles, soreness in the mouth without signs of stomatitis in one patient, transient mild diarrhea in 2 patients, mild phlebitis at the infusion site in 1 patient, and local urticaria following the distribution of the vein used for administration of the drug in 2 patients. In one patient, administration of another 25 mg of benadryl i.v. alleviated the urticaria on 2 separate occasions. Treatment was interrupted in the second patient and was discontinued altogether when local urticaria developed on repeat administration of rubidazone. No systemic allergic reactions or evidence of cardiac toxicity were noted.

One patient experienced a 4-month partial regression of abdominal and supraclavicular nodal metastases from an adenocarcinoma of unknown origin. None of the remaining patients had objective tumor response. Assay of Rubidazone. Our HPLC method separated rubidazone, daunorubicin, daunorubicinol, and the aglycone of daunorubicin (Chart 2). The first 3 compounds could be measured at plasma concentrations from 0.1 to 10 μM (~60 ng to 6 μg/ml plasma). The lower limit of detection was approximately 20 ng/ml. Chart 3 shows a standard curve of the ratios of peak areas of varying amounts of rubidazone to peak areas of a constant amount of daunorubicinol (internal standard) versus mubidazone concentration in extracts of plasma standards. A ratio of 1:1 was found at equimolar concentrations of rubidazone and internal standard. Standard curves of rubidazone and daunorubicin extracted from plasma in the presence or absence of daunorubicinol were identical. The aglycone eluted with the solvent front and could not be measured in butanol extracts of plasma which contain fluorescent nonnaphthacycline substances that coelute with the aglycone.

Tris-HCl, pH 7.6, in the mobile solvent maintained the stability of rubidazone on the column and enhanced separation compared to mobile solvent containing water instead of buffer. Use of buffers below pH 7.0 produced sharper peaks but caused breakdown of rubidazone to daunorubicin. Mobile solvents more basic than pH 8.0 caused progressive deterioration in column performance. Reverse-phase (C<sub>18</sub> or C<sub>18</sub>-bonded phase), silica, and alumina columns either bound rubidazone essentially irreversibly or gave poor separations with a variety of solvent systems. Maximum sensitivity of measurement of the anthracyclines was 0.1 μM using a Schoeffel Model 970 fluorescence detector at an excitation wavelength of 252 nm and measurement of fluorescence above 520 nm (cutoff filter). Total fluorescence measurements of standard solutions and

<table>
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<th>Patient</th>
<th>Age</th>
<th>Sex</th>
<th>Status</th>
<th>Primary tumor</th>
<th>Prior therapy</th>
<th>WBC nadir&lt;sup&gt;b&lt;/sup&gt;</th>
<th>RBC nadir&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Hb&lt;sup&gt;c&lt;/sup&gt;</th>
<th>PLT nadir&lt;sup&gt;b&lt;/sup&gt;</th>
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<td>1</td>
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<td>59</td>
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<td>2</td>
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<td>2</td>
<td>Duodenum</td>
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<td>560</td>
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<td>428</td>
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<tr>
<td>4</td>
<td>53F</td>
<td>1</td>
<td>Colon</td>
<td>Chemotherapy</td>
<td>731</td>
<td>Normal</td>
<td>629</td>
<td>Normal</td>
<td>94</td>
<td>Normal</td>
</tr>
<tr>
<td>5</td>
<td>61M</td>
<td>3</td>
<td>Colon</td>
<td>Chemotherapy + radiotherapy</td>
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<td>Normal</td>
<td>94</td>
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<tr>
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<td>43F</td>
<td>1</td>
<td>Colon</td>
<td>Chemotherapy</td>
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<td>629</td>
<td>Normal</td>
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<td>Normal</td>
</tr>
<tr>
<td>7</td>
<td>55M</td>
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<td>Colon</td>
<td>Chemotherapy</td>
<td>428</td>
<td>Normal</td>
<td>629</td>
<td>Normal</td>
<td>94</td>
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<tr>
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<td>94</td>
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<td>55F</td>
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<td>31</td>
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<td>Normal</td>
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</tbody>
</table>

<sup>a</sup> Eastern Cooperative Oncology Group Scale (0, fully active, to 4, totally disabled).
<sup>b</sup> Upper limit of normal, 250 units/liter.
<sup>c</sup> Upper limit of normal, 20 units/liter.
Assays of known concentrations of rubidazone, daunorubicin, and daunorubicinol in butanol extracts of pooled human plasma by measurement of total fluorescence. Extractions were carried out as described in text. Excitation was carried out at 470 nm, and emission was measured at 554 nm against an extract of control plasma using an Aminco Bowman spectrophotometer. Total fluorescence of plasma extract (arbitrary units)

<table>
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<tr>
<th>Plasma concentration (M)</th>
<th>Rubidazone</th>
<th>Daunorubicin</th>
<th>Daunorubicinol</th>
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<tr>
<td>10^{-4}</td>
<td>1620</td>
<td>1575</td>
<td>1560</td>
</tr>
<tr>
<td>5 × 10^{-5}</td>
<td>822</td>
<td>850</td>
<td>910</td>
</tr>
<tr>
<td>10^{-5}</td>
<td>185</td>
<td>184</td>
<td>194</td>
</tr>
<tr>
<td>5 × 10^{-6}</td>
<td>88</td>
<td>94</td>
<td>107</td>
</tr>
<tr>
<td>10^{-6}</td>
<td>19</td>
<td>18</td>
<td>20</td>
</tr>
<tr>
<td>5 × 10^{-7}</td>
<td>9.7</td>
<td>10</td>
<td>11</td>
</tr>
<tr>
<td>10^{-7}</td>
<td>3.6</td>
<td>4.2</td>
<td>3.4</td>
</tr>
<tr>
<td>5 × 10^{-8}</td>
<td>2.4</td>
<td>3.4</td>
<td>2.3</td>
</tr>
<tr>
<td>10^{-8}</td>
<td>1.4</td>
<td>1.0</td>
<td>1.0</td>
</tr>
</tbody>
</table>

plasma extracts of the anthracyclines with an Aminco Bowman or SLM spectrofluorometer were maximum at an excitation wavelength of 470 nm and emission monitored at 554 nm. As shown in Table 2, the lower limit of accurate measurement by total fluorescence of rubidazone, daunorubicin, or daunorubicinol in butanol extracts of human plasma was 0.1 μM (~60 ng/ml) with slight loss of linearity between 0.5 and 0.1 μM. This is in agreement with the original report of this method by Finkel et al. (6) for daunorubicinol and a recent report by Pacciarini et al. (13) for daunorubicin and Adriamycin. Fluorescence in excess of that in extracts of control plasma was detected at plasma concentrations of rubidazone, daunorubicin, or daunorubicinol as low as 0.01 μM but was not linearly related to concentrations below 0.1 μM. Butanol extracts of pooled normal plasma compared to standards of rubidazone or daunorubicin dissolved in butanol contained substances producing fluorescence equivalent to a 0.1 μM solution of anthracycline. Sensitivity of detection was not affected by omitting the sodium hydroxide from the extraction procedure. Acid:alcohol extracts of known standards of rubidazone or daunorubicin were comparable to butanol extracts both in sensitivity of detection and in amount of non-anthracycline-fluorescent materials present in control plasma. Standard solutions of rubidazone or daunorubicin in butanol or in 75% ethanol:0.45 N HCl were linear from approximately 0.01 to 10 μM as determined by photon counting in an SLM spectrofluorometer.

Recoveries of rubidazone, daunorubicin, or daunorubicinol from plasma by butanol extraction ranged from 75% at 0.1 μM to 85% at 10 μM. Substitution of water for 0.01 N sodium hydroxide in the extraction procedure did not alter recoveries as determined by total fluorescence of extracts but resulted in retention of small amounts of all 3 compounds on the HPLC column.

Rubidazone and daunorubicin were stable in heparinized human plasma and in butanol extracts of plasma stored at −70° for at least 1 year. However, concentration of the sodium hydroxide:butanol extracts to dryness under nitrogen produced variable and extensive (30 to 70%) destruction of rubidazone and some (~10%) decrease in total.
fluorescence. Concentration of water:butanol extracts resulted in variable losses of drug (~5 to 10%) but did not cause breakdown of rubidazole to daunorubicin.

TLC using either solvent system, chloroform:methanol:14% ammonium hydroxide or chloroform:methanol:water, satisfactorily resolved rubidazone, daunorubicin, daunorubicinol, and daunorubicinone. Recoveries of the compounds by scraping the silica from the plates and elution with ethanol were variable. Some conversion of rubidazole to daunorubicin invariably occurred, suggesting instability of rubidazole on silica plates.

**Assay of Formulated Product.** The formulated product contained approximately 10% (range, 6 to 11%) daunorubicin and 90% rubidazole by HPLC assay. These percentages were the same whether the formulated product was dissolved in the sodium glycinate buffer supplied by the manufacturer, in ethanol, in butanol, or in Tris-HCl buffer, pH 7.6 to 9.0. When the formulated product was dissolved in buffer at a pH less than 7.0 or in unbuffered 0.9% NaCl or dextrose solutions, rubidazole was unstable. When the formulated product was dissolved in sodium glycinate buffer and diluted in 5% dextrose in water to a final concentration of 1 mg/ml, the proportion of rubidazole remained constant at approximately 9:1 for at least 3 hr at room temperature under conditions of normal room lighting.

The plasma concentrations of rubidazole and daunorubicin were studied in 6 patients receiving 100 to 150 mg/sq m rubidazole i.v. over 1 hr. The only compounds detected with the fluorescence characteristics of anthracyclines were rubidazone and daunorubicin. Daunorubicinol was not present in any sample (lower limit of detection, 20 ng/ml plasma). Rubidazole, as measured by HPLC, accounted for at least 90% of the total anthracycline present as measured by total fluorescence of plasma extracts prepared by the butanol method or the acid:alcohol method. Peak plasma concentrations of rubidazole and daunorubicin were achieved within 15 min after beginning the 1-hr infusion, remained at approximately that level until termination of the infusion, and then declined. Table 3 shows the plasma concentrations of rubidazole and daunorubicin measured by HPLC and the concentration of total anthracycline equivalents measured by total fluorescence during and for 2 hr after the infusion of rubidazole at 150 mg/sq m. The total anthracyclines present are accounted for by rubidazole and daunorubicin. Chart 4 shows the concentrations of rubidazole in another patient receiving 150 mg/sq m measured by HPLC analysis and total fluorescence. After determining that no daunorubicinol could be detected in any sample up to 7.5 hr after infusion, analysis of this patient's samples was repeated using daunorubicinol as an internal standard. Plasma with and without the internal standard was extracted and analyzed by HPLC. Plasma without internal standard was analyzed by measurement of total fluorescence. Concentrations of rubidazole calculated either by the ratio of rubidazole to the internal standard or by comparison to a standard curve of rubidazole accounted for 90% or more of the total anthracycline present during infusion and for at least the next hr as determined by total fluorescence.

**DISCUSSION**

The major toxicity of rubidazole given by 1 hr infusion was myelosuppression, with 12 of 14 patients treated at 150 mg/sq m having nadirs of leukopenia less than 4000 cells/cu mm and 7 of 14 patients having nadirs less than 3000 cells/cu mm. Thrombocytopenia was rare. Recovery from leukopenia occurred 21 to 28 days after treatment. We recommend 150 mg/sq m every 3 to 4 weeks for initiating Phase 2 studies in patients with solid tumors.

Our HPLC assay allows rapid measurement of rubidazole, daunorubicin, and daunorubicinol in standard preparations of the drugs and in human plasma. Pharmaceutical preparations of rubidazole used in this study contained from 6 to 11% daunorubicin. We found that the ratio of rubidazole to daunorubicin in the formulated product was maintained for several hr in vivo. In no instance did daunorubicinol levels increase with time relative to rubidazole levels or relative to total fluorescence up to 6 hr after drug administration. No daunorubicinol was found during this time period. These observations demonstrate that rubida-

**Table 3**

<table>
<thead>
<tr>
<th>Time (min) from start of 60-min infusion</th>
<th>Daunorubicin (µg/ml)</th>
<th>Rubidazole (µg/ml)</th>
<th>Concentration of Rubidazole (µg/ml) by Total Fluorescence of Anthracycline Equivalents</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>15</td>
<td>0.6</td>
<td>5.8</td>
<td>4.8</td>
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<tr>
<td>30</td>
<td>0.5</td>
<td>5.5</td>
<td>6.3</td>
</tr>
<tr>
<td>45</td>
<td>0.5</td>
<td>5.7</td>
<td>6.0</td>
</tr>
<tr>
<td>60 (end infusion)</td>
<td>0.07</td>
<td>0.63</td>
<td>0.9</td>
</tr>
<tr>
<td>90</td>
<td>&lt;0.05</td>
<td>0.36</td>
<td>0.4</td>
</tr>
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<td>120</td>
<td></td>
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</tbody>
</table>
zone is not rapidly converted to daunorubicin in vivo.

Using the HPLC assay or the total fluorescence assay, we were unable to quantitate rubidazole for periods sufficiently long to characterize the terminal phase(s) of elimination. Linearity of standard curves measured by total fluorescence was lost at concentrations lower than 0.1 μM, although fluorescence above background was detectable. We have been unable to develop a TLC method which does not produce variable losses of drug and variable conversion of rubidazole to daunorubicin.

We chose to administer rubidazole by 1-hr infusion since rapid administration has been associated with acute allergic anaphylactoid reactions (8). Although we have not measured peak levels after rapid injection, it is reasonable to assume that plasma concentrations achieved by 1-hr infusion are considerably lower than when the same total dose is given by rapid injection. Fractionated doses of Adriamycin have been reported to be as therapeutically effective as but less cardiotoxic than the same total dose of Adriamycin given as a single injection. Recently, Pacciarini et al. (13) showed in tumor-bearing mice that fractionated doses of Adriamycin (and daunorubicin) result in lower concentrations of drug in myocardial tissue than does a single dose of the same total amount of drug. Antitumor activity was comparable with both schedules of administration. Myocardial concentrations of Adriamycin were directly related to plasma concentrations, whereas tumor concentrations were dependent on total amount of drug administered.

If rubidazole is found to have therapeutic activity comparable to daunorubicin (or Adriamycin), comparative studies of antitumor activity and cardiac toxicity will be of interest. It appears that such studies should consider plasma concentrations achieved as a function of the total dose, schedule, and rate of administration of the drugs.

REFERENCES

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