Chronic Cardiotoxicity Studies in Rabbits with 7-con-O-Methylnogarol, a New Anthracycline Antitumor Agent

J. Patrick McGovren, Gary L. Neil, Robert H. Denlinger, Thomas L. Hall, Sheri L. Crampton, and James A. Swenberg

Research Laboratories, The Upjohn Company, Kalamazoo, Michigan 49001

ABSTRACT

7-con-O-Methylnogarol (7-OMEN), a new analog of the anthracycline antibiotic, nogalamycin, has chemotherapeutic activity in several experimental mouse tumor systems. As part of the preclinical development of 7-OMEN, the cardiotoxic potential was evaluated in chronically dosed rabbits. Groups of 4 rabbits were dosed twice weekly i.v. with 11 or 33 mg/sq m/week for 12 or 24 weeks, or 154 mg/sq m/week for 24 weeks to give cumulative doses of 132, 396, 1319, 2640, or 3700 mg/sq m, respectively. Histological studies showed minimal evidence of cardiotoxicity in rabbits which received 1319 mg/sq m or lower doses of 7-OMEN. However, the characteristic anthracycline-induced cardiac lesions (vacuolization, myocytolysis, and fibrosis) were present in mild to marked amounts in 8 of 8 rabbits which received cumulative doses of 2640 or 3700 mg/sq m. One rabbit in the 3700 mg/sq m group exhibited excess pericardial fluid; no other gross symptoms of cardiac toxicity were present. None of the 7-OMEN-treated rabbits died from cardiotoxicity. Four Adriamycin-treated control rabbits died of drug-induced cardiomyopathy and congestive heart failure at 222 to 277 mg/sq m. Thus, 7-OMEN was less than one-fifteenth as potent as was Adriamycin in inducing cardiotoxicity in rabbits.

7-OMEN given at 220 mg/sq m/week for 3 to 4 weeks caused lethal bone marrow depression in 4 of 4 rabbits. At lower doses, 7-OMEN caused a mild to moderate, dose-related, regenerative, macrocytic anemia which was most severe approximately halfway through the 24-week study and then improved despite continuous twice-weekly dosing.

INTRODUCTION

7-OMEN (U-52,047; NSC 269148) is one of a series of analogs of the anthracycline antibiotic, nogalamycin (Refs. 16 and 17; Chart 1). 7-OMEN is active against a number of experimental mouse tumors, including the P388 and L1210 leukemias and the B16 melanoma (11, 12). 7-OMEN has structural and biochemical properties which distinguish it from other anthracycline antitumor agents, including Adriamycin. These properties suggest that 7-OMEN may have a different mechanism of cytotoxic action (2, 8, 9).

The success of Adriamycin and daunomycin in the treatment of human cancer is limited by a well-characterized but poorly understood cardiomyopathy which occurs in a high proportion of patients exceeding cumulative doses of 550 and 650 mg/sq m, respectively (7, 10). Two Adriamycin analogs currently in clinical trials are also known or suspected to induce cardiotoxicity, namely, rubidazole, which has been reported to be cardiotoxic in humans at cumulative doses of greater than 1500 mg/sq m (1, 5), and AD-32, which causes cardiac lesions in rabbits (3). Thus, any new anthracycline analog proposed for clinical trials must be evaluated for its cardiotoxic potential.

Since rabbits reproducibly develop anthracycline-induced cardiomyopathy and congestive heart failure characteristic of clinical toxicity following chronic administration, this species has been widely used as a model (6, 13, 19) and was chosen for the studies on 7-OMEN. Most anthracycline compounds are also quite myelosuppressive; therefore, doses must be carefully adjusted to avoid killing the animals from bone marrow toxicity before appropriate cumulative doses are administered.

MATERIALS AND METHODS

Animals. All toxicity studies were conducted with male and female New Zealand white rabbits. Animals used in the acute lethality determination and in the 12-week cardiotoxicity study were purchased from Lyle Waite, Otsego, Mich., and weighed 2.4 to 3.8 kg at the outset of the studies. The rabbits used in the 24-week cardiotoxicity study were specific-pathogen-free animals (Dutchland Laboratory Animals, Denver, Pa.) and weighed 2.7 to 3.5 kg at the start of the study. In all studies, males and females were equally distributed in the treatment groups. The rabbits in each experiment were housed individually and kept in an environment isolated from other animals. In the acute lethality and 12-week cardiotoxicity studies, they were fed Purina rabbit chow (Ralston Purina Co., St. Louis, Mo.) and water ad libitum. In the 24-week cardiotoxicity study, food was allowed ad libitum for 10 weeks and was then rationed at 90 g/day to all groups for the remainder of the study to maintain body weight at 3 to 4 kg.

Drugs. 7-OMEN was prepared by chemical modification of the anthracycline antibiotic nogalamycin by Dr. P. F. Wiley at The Upjohn Co., Kalamazoo, Mich. (17, 18) and was 80 to 90% pure in the acute lethality and 12-week cardiotoxicity studies. The impurity present in this material was the compound nogarene (17). Nogarene has low therapeutic activity in experimental mouse tumor systems (12). The material used in the 24-week study was at least 98% pure and contained no detectable nogarene. Little is known of the toxicity of nogarene; however, evidence presented below suggests that nogarene is...
Drug Administration. Doses were based on individual animal weights on the day of drug administration. The conversion factor, 0.091 sq kg/mg, was used to convert mg/kg doses to mg/sq m. Both 7-OMEN and Adriamycin were administered as the appropriate volume of 2.5 mg/ml solution in aqueous 0.01 m glucuronic acid (Sigma Chemical Co., St. Louis, Mo.) containing 5% glucose. In all studies, 7-OMEN solutions (2.5 mg/ml) were infused into the ear veins at 0.7 ml/min using a Harvard Model 940 infusion pump (Harvard Apparatus Co., Millis, Mass.). In a pilot study, i.v. infusion of a 7-OMEN solution (10 mg/ml) at 0.18 ml/min caused immediate death. Adriamycin was injected i.v. over a 30-sec period.

7-OMEN solutions were prepared 12 to 18 hr before administration and refrigerated until use or were prepared and used immediately. The drug was shown by thin-layer chromatography to be stable under these conditions. Adriamycin solutions were always prepared just prior to administration.

To minimize local tissue reactions, the injection sites in the marginal and medial ear veins of the left and right ears were alternated as much as possible. Extravasation of 7-OMEN resulted in local inflammation and scarring as previously noted for Adriamycin (19). On one occasion, an accidental i.a. injection of 7-OMEN was made, and the entire ear became necrotic within a few days.

Acute Lethal Toxicity Study. In the acute study, groups of 2 rabbits received single i.v. doses of 30, 60, and 100 mg/kg (330, 659, and 1099 mg/sq m), and 4 rabbits received 45 mg/kg (495 mg/sq m). At the solution concentration and infusion rate described above, the duration of the infusions was approximately 50 to 170 min for these doses. The animals were observed daily until death or for 16 days and necropsied. Hematology and blood chemistry studies were performed 5 days after dosing and just prior to necropsy on animals receiving the 330- and 495-mg/sq m doses.

Cardiotoxicity Studies. In the 12-week cardiotoxicity study, groups of 4 rabbits were dosed with 7-OMEN [1, 3, 10, or 20 mg/kg/week (11, 33, 110, or 220 mg/sq m/week)] in 2 divided doses or a volume of vehicle equivalent to that administered to the 220 mg/sq m-treated group. In the 24-week study, groups of 4 or 6 rabbits were dosed with Adriamycin [2 mg/kg/week (22 mg/sq m/week)], 7-OMEN [10 or 14 mg/kg/week (110 or 154 mg/sq m/week)] in 2 divided doses or a volume of vehicle equivalent to that administered to the 154 mg/sq m/week-treated group. At the solution concentration and infusion rate described above, the duration of the 7-OMEN infusions was approximately 1 to 12 min/injection at these doses. One dose was not given during the 12th week of the 24-week study because the Great Blizzard of 1978 prevented personnel from getting to work. For this reason, an additional dose was administered in the 25th week.

In both cardiotoxicity studies, arterial blood samples were drawn from the ear at 2-week intervals throughout the study for hematology and chemistry studies. Hematological measurements included WBC, RBC, hemoglobin concentration, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, differential leukocyte count, nucleated RBC, reticulocyte count (Weeks 10 to 25 only), and platelet count. Blood chemistry studies were carried out on a Technicon Auto Analyzer SMA 12/60 and included analyses for calcium, inorganic phosphate, glucose, blood urea nitrogen, uric acid, cholesterol, albumin, total pro-
tein, total bilirubin, alkaline phosphatase, serum glutamic-oxaloacetic transaminase, and lactic dehydrogenase. Manual blood chemistry analyses were performed for serum glutamic-pyruvic transaminase, sodium, potassium, chloride, and, on terminal samples only, creatine phosphokinase.

At the termination of the studies, rabbits were anesthetized with pentobarbital or CO₂. Blood samples were drawn from the abdominal aorta, and the animals were exsanguinated. Complete necropsy was performed on all animals. Organ weights were measured for liver, kidneys, heart, adrenals, testes, and spleen. Tissues were fixed for light microscopy in 10% neutral buffered formalin. In the 12-week study, only hearts were examined histologically. In the 24-week study, a standard protocol of 40 tissues was examined histologically, including 3 sections of heart. Sections were cut at 6 μm and stained with hematoxylin and phloxine (all tissues) and Oil Red O (heart, kidney, and liver). Heart sections were also stained with Mason’s trichrome.

Statistical Methods. Significance testing was carried out on the erythrocyte and leukocyte count and mean corpuscular volume data at −2, 4, 8, 12, 17, and 24 weeks; pairwise comparisons of the treated groups to the vehicle control group were made with the least significant difference method on estimated means using the mean square error term from a one-way analysis of variance (15). Organ weights as a percentage of final body weight were compared to vehicle controls using the 2-tailed Student t test (15).

RESULTS

Acute Lethality Study

Because of the limited number of animals studied, a precise LD₅₀ was not determined. However, these preliminary experiments indicated that the LD₅₀ was within the range of 330 to 659 mg/sq m with 495 mg/sq m killing 2 of 4 rabbits within 7 days. The surviving rabbits receiving 495 mg/sq m and both rabbits receiving 330 mg/sq m were sacrificed and necropsied 16 days after dosing. Both animals in each of the 659- and 1099-mg/sq m dose groups died 5 to 7 days after dosing. The cause of death was determined to be massive hemorrhage. Petechial hemorrhages were seen in the lungs of one rabbit receiving 330 mg/sq m; however, the other survivors of the 330- and 495-mg/sq m dose groups showed no gross lesions. Blood counts performed 5 days after dosing in the 495-mg/sq m group showed a 60 to 70% depression of leukocytes and 75 to 95% depression of platelets (Table 1). Both leukocyte and platelet counts had returned to normal in the 2 surviving rabbits receiving 495 mg/sq m by Day 16.

<table>
<thead>
<tr>
<th>Rabbit</th>
<th>WBC[^a]</th>
<th>Platelets[^a]</th>
<th>WBC</th>
<th>Platelets</th>
</tr>
</thead>
<tbody>
<tr>
<td>1[^b]</td>
<td>7.7</td>
<td>300</td>
<td>3.0</td>
<td>40</td>
</tr>
<tr>
<td>2[^b]</td>
<td>6.4</td>
<td>320</td>
<td>2.1</td>
<td>50</td>
</tr>
<tr>
<td>3[^b]</td>
<td>2.8</td>
<td>15</td>
<td>16.1</td>
<td>40</td>
</tr>
<tr>
<td>4[^c]</td>
<td>2.9</td>
<td>80</td>
<td>10.7</td>
<td>365</td>
</tr>
</tbody>
</table>

[^b] 10[^10] platelets/cu mm
[^c] Died on Day 7.

12-Week Cardiotoxicity Study

In the 12-week cardiotoxicity study, all animals in the 220-mg/sq m/week dose group died from hemorrhage by the fourth week of dosing. Platelet counts were depressed by 90% just before death. Leukocytes and erythrocytes were also markedly depresses. In the 11-, 33-, and 110-mg/sq m/week dose groups (corresponding to 132, 396, and 1319 mg/sq m total dose), the animals gained weight in parallel to vehicle controls. No significant differences in organ weights were observed between drug-treated and control groups. Moderate to severe local reactions occurred at the injection sites. In the 110-mg/sq m/week dose group, the only hematological effects noted were transient decreases in erythrocyte and platelet counts. No hematological effects were noted in lower dose or vehicle control groups. Histological studies on the hearts showed 2 small foci of fibrosis in the left ventricle of one rabbit receiving 11 mg/sq/m/week, scattered small foci of fibrosis in the papillary muscle of 2 animals receiving 33 mg/sq m/week, scattered small foci of fibrosis in the left ventricle of one rabbit receiving 110 mg/sq m/week, possible vacuolization of scattered myocytes of one other animal receiving 110 mg/sq m/week. No evidence of cardiotoxicity was detected in 3 of the rabbits which died of myelotoxicity following 220 mg/sq m/week; however, autolysis precluded extensive evaluation. One rabbit receiving 220 mg/sq m/week (550-mg/sq m cumulative dose) had minimal autolysis and slight fibrosis of the interventricular septum near the arteriovenous valves. The location and type of lesion present in this particular animal were similar to those seen in the 24-week study.

24-Week Cardiotoxicity Study

Body and Organ Weights. In the 24-week study, both groups treated with 7-OMEN (110 and 154 mg/sq m/week) (corresponding to 2640 and 3700 mg/sq m total dose) gained weight in parallel to the vehicle control rabbits (Chart 2). Severe wasting was evident in Adriamycin-treated rabbits by the fourth week of treatment. Weight of adrenals as a percentage of final body weight was significantly lower in both groups of 7-OMEN-treated rabbits compared to controls (p < 0.05). As a percentage of final body weight, Adriamycin-treated rabbits had...
higher heart, liver, and kidney weights and lower testes weights (p < 0.05).

Hematology and Blood Chemistry. Hematological studies were performed at 2-week intervals throughout the 24-week study. 7-OMEN-induced leukopenia was dose related but moderate (Chart 3). At the end of the study, platelet counts were depressed approximately 50% in both 7-OMEN-treated groups. Platelet counts never fell below 220 x 10^3/cu mm. A dose-dependent regenerative macrocytic anemia was induced by 7-OMEN. Charts 4 and 5 show the time course of erythrocyte counts and mean corpuscular volumes. Only moderate changes were seen in erythrocyte counts, hemoglobin concentration, mean corpuscular volumes, and hematocrits in the group receiving 110 mg/sq m/week. However, in the 154 mg/sq m/week dose group, the anemia was more severe, and one rabbit expired in the 15th week of treatment due to hypoxic liver necrosis. This rabbit’s erythrocyte count was 1.7 x 10^6/cu mm, and hemoglobin concentration was 3.2 g/100 ml when moribund. In all the other animals receiving 154 mg/sq m/week, the anemia reached a nadir during the tenth week of dosing and then improved despite continuous twice-weekly dosing. The improvement was also evident in the time course of the mean corpuscular volume (Chart 5). The rapid reversibility of the anemia was demonstrated when one dose was not administered in the 12th week, and both 7-OMEN-treated groups showed sharp rises in erythrocyte count, hemoglobin concentration, and hematocrit the next week. By the 14th week, 5 more doses had been given, and these measurements had declined again. The sudden increase in average erythrocyte count evident in the 154-mg/sq m/week dose groups in the 17th week is a reflection of the death of the rabbit which had the most severe anemia. Increased nucleated RBC counts were observed in both 7-OMEN dose groups. Reticulocyte counts were begun in the tenth week and were elevated throughout the remainder of the study.

Chart 3. Time course of rabbit leukocyte counts (mean of 4 to 6 rabbits per point). The means of the relative S.D.’s at each time point for each treatment group were: for vehicle controls, 15.9%; for Adriamycin-treated rabbits, 25.9%; for rabbits treated with 154 mg/sq m/week, 25.5%; and for rabbits treated with 7-OMEN (154 mg/sq m/week), 28.0%. Statistical significance testing at —2, 4, 8, 12, 17, and 24 weeks showed significantly decreased erythrocyte counts compared to controls (p < 0.05) at 8 weeks, in Adriamycin-treated groups, at 24 weeks in groups treated with 7-OMEN (110 mg/sq m/week), and at 8, 12, and 17 weeks in the groups treated with 7-OMEN (154 mg/sq m/week).

Blood chemistry evaluations demonstrated minimal treatment effects. Serum calcium of Adriamycin-treated rabbits was low, and serum cholesterol was high compared to control values just before death.

Gross Observations. No significant gross lesions were noted in control rabbits. Slight to extensive ascites was present in 3 of 4 Adriamycin-treated animals. Similarly, 3 of 4 of the animals on this treatment had livers with a prominent lobular pattern. The testes of both Adriamycin-treated males were small and flabby. One rabbit in this treatment group had acute pancreatitis. Gross cardiac lesions were noted in 3 of 4 rabbits treated...
with Adriamycin. Pale, flabby to fibrotic hearts were noted in 3, while excess pericardial fluid was detected in only one. Mid-dorsal alopecia and dry skin were present on 3 of 4 rabbits receiving Adriamycin.

One rabbit receiving 7-OMEN (110 mg/sq m/week) died of a fractured spine in the fifth week. Extensive hemorrhage was present in the adjacent tissue. Two of 6 rabbits treated with 7-OMEN (154 mg/sq m/week) died during the study, one in the fifth week with acute pulmonary edema and one in the 14th week with hypoxic liver necrosis. The thorax of the latter animal contained excessive fluid. One rabbit completing the study had increased pericardial fluid, hemorrhage, and congestion of the lungs.

Histopathological Observations. Histopathological studies of the hearts of rabbits treated with 7-OMEN revealed mild to marked cardiomyopathy which was dose related (Table 2). The lesions tended to be localized in the interventricular septum and left ventricle near the arteriovenous valves. The cardiomyopathy was characterized by vacuolization of myocytes and fibrosis (Fig. 1a). The latter was particularly prominent in slides stained by the Masson’s trichrome method. Mild lesions were usually perivascular, whereas more extensive lesions were generalized. The rabbit receiving 110 mg/sq m/week with the fractured spine had no heart lesions (cumulative dose, 550 mg/sq m). The rabbit receiving 154 mg/sq m/week that died of pulmonary edema after receiving 769 mg/sq m had mild perivascular fibrosis and vacuolization of the heart (histological score, 1). The rabbit that died of hypoxic liver necrosis after receiving 2231 mg/sq m had no heart lesions. Hearts from Adriamycin-treated rabbits exhibited similar, but more extensive cardiomyopathy (Table 2; Fig. 1b). In one animal, the lesions extended into the atrium. No evidence of cardiomyopathy was seen in hearts of control rabbits.

Other histological findings included degeneration and atrophy of seminiferous tubules of the males treated with Adriamycin and 7-OMEN (154 mg/sq m/week). These changes were not apparent in the 2 males which received 7-OMEN (110 mg/sq m/week) or in control rabbits. Kidneys of some rabbits treated with 7-OMEN had mild fatty infiltration of the tubules. Occasional hyaline casts were also detected in these animals. Glomerular adhesions and hyaline casts occurred in 4 of 4 rabbits treated with Adriamycin.康复Animals treated with 7-OMEN exhibited normal bone marrow cellularity (Grade 2) and the presence of active red and white pulp in the spleens of all rabbits receiving 110 mg/sq m/week. One rabbit which received 154 mg/sq m/week had slight hypoplasia of the spleen, 2 had mild hypoplasia, and 2 were normal. All 4 Adriamycin-treated animals had mild splenic hypoplasia and hypoplasia of the bone marrow (Grade 1 cellularity). Although adrenal weights in 7-OMEN-treated rabbits were significantly lower than controls, no significant abnormalities were detected histologically. Lesions at the injection sites varied from mild-to-moderate perivascular fibrosis and occasional abscesses in 7-OMEN-treated rabbits. Mild perivascular fibrosis was also detected in the ears of several control and Adriamycin-treated rabbits.

DISCUSSION

7-OMEN administered chronically to rabbits caused cardiac lesions characteristic of anthracyclines in a dose-dependent fashion (Fig. 1). At cumulative doses of 2640 and 3700 mg/sq m, 8 of 8 rabbits exhibited mild-to-severe heart lesions (Table 1), and one rabbit in the 3700-mg/sq m dose group exhibited excess pericardial fluid. No other gross symptoms of heart failure were present. The heart lesions appearing in these 2 dose groups and in the Adriamycin-treated control group were usually perivascular and were frequently located in the interventricular septum and left ventricle near the arteriovenous valves. Mild cardiac lesions (histological score, 1) were observed in 5 of 12 animals receiving doses of 132, 396, and 1319 mg/sq m; however, these did not occur at the characteristic site of Adriamycin and higher-dose, 7-OMEN-induced lesions, suggesting that the damage may not have been drug induced. However, similar lesions were not observed in 8 vehicle control hearts. One rabbit which died of myelosuppression after receiving 220 mg/sq m/week for 2.5 weeks (cumulative dose, 550 mg/sq m) had a mild lesion of the type and location seen in the 24-week study. One rabbit receiving 154 mg/sq m/week died with acute pulmonary edema after 5 weeks of dosing (cumulative dose, 769 mg/sq m). Its heart contained mild perivascular myocytolysis and fibrosis (score, 1). The cardiac damage did not appear to be severe enough to have caused the animal’s death. Two other rabbits which died early (550 and 2231 mg/sq m cumulative doses) had no heart lesions.

All Adriamycin-treated control rabbits (4 of 4) died of drug-induced cardiomyopathy and congestive heart failure at 222 to 277 mg/sq m. No 7-OMEN-treated rabbits died from cardiotoxicity at doses to 3700 mg/sq m; thus 7-OMEN is less than one-fifteenth as potent as is Adriamycin in inducing cardiotoxicity in rabbits. Depending on the tumor system and the dose, schedule, and route of drug administration, 7-OMEN is 6 to 12 times less potent than is Adriamycin in the treatment of experimental mouse tumors (12). Since 7-OMEN is at least 15 times less potent than is Adriamycin in inducing cardiotoxicity, 7-

---

Table 2

<table>
<thead>
<tr>
<th>Agent</th>
<th>Cumulative dose (mg/sq m)</th>
<th>Schedule</th>
<th>Individual scores</th>
<th>Av. score</th>
</tr>
</thead>
<tbody>
<tr>
<td>7-OMEN</td>
<td>132</td>
<td>wk</td>
<td>0-0-0-1</td>
<td>&lt;1</td>
</tr>
<tr>
<td></td>
<td>396</td>
<td>wk</td>
<td>0-0-1-1</td>
<td>&lt;1</td>
</tr>
<tr>
<td>7-OMEN</td>
<td>1319</td>
<td>wk</td>
<td>0-0-1-1</td>
<td>&lt;1</td>
</tr>
<tr>
<td>7-OMEN</td>
<td>2640</td>
<td>wk</td>
<td>1-1-2-1</td>
<td>1.3</td>
</tr>
<tr>
<td>7-OMEN</td>
<td>3700</td>
<td>wk</td>
<td>2-2-2-4</td>
<td>2.5</td>
</tr>
<tr>
<td>Adriamycin</td>
<td>222-277</td>
<td>wk</td>
<td>2-4-4-3</td>
<td>3.3</td>
</tr>
</tbody>
</table>

* Some animals did not complete the study. One rabbit died as a result of hypoxic liver necrosis after receiving 7-OMEN (2223 mg/sq m) as 154 mg/sq m/week for 14.5 weeks; this animal’s histological score was 0. Another rabbit died with pulmonary edema after receiving 7-OMEN (769 mg/sq m) as 154 mg/sq m/week for 5 weeks; this animal’s histological score was 1. One rabbit receiving 110 mg/sq m/week died of a broken back in the fifth week (cumulative dose; 550 mg/sq m); no heart lesions were present.
OMEN could possess a therapeutic advantage over Adriamycin.

7-OMEN given at 220 mg/sq m/week caused lethal bone marrow depression in 4 of 4 rabbits in 3 to 4 weeks. At lower doses (110 to 154 mg/sq m/week), the myelotoxicity was less severe and appeared to be rapidly reversible, as demonstrated by increases in erythrocyte counts when one dose was missed in the 12th week of the 24-week study (Chart 1). 7-OMEN caused a dose-related regenerative macrocytic anemia which was most severe approximately halfway through the 24-week doses (110 to 154 mg/sq m/week), the myelotoxicity was less severe and appeared to be rapidly reversible, as demonstrated by increases in erythrocyte counts when one dose was missed in the 12th week of the 24-week study (Chart 1). 7-OMEN caused a dose-related regenerative macrocytic anemia which was most severe approximately halfway through the 24-week study and then improved despite continuous biweekly dosing (Charts 4 and 5). The regenerative nature of the myelotoxicity was also supported by normal cellularity of bone marrow and the presence of active red and white pulp in spleens of rabbits treated with 7-OMEN (110 to 154 mg/sq m/week).

Previous investigators have noted renal toxicity induced by Adriamycin in chronically treated rabbits (19). In this study, 4 of 4 Adriamycin-treated rabbits exhibited protein casts and other evidence of toxic glomerulonephritis. Mild nephropathy characterized by fatty infiltration of tubules, vacuolated tubular epithelial cells, and occasional protein casts was also present in some 7-OMEN-treated animals. In all instances, the lesions in 7-OMEN-treated rabbits were milder than were those induced by Adriamycin.

7-OMEN differs in chemical structure from other anthracycline antitumor agents in several respects (Chart 1). Among other things, it has a methoxyl rather than a sugar attached at the 7-carbon position on the A ring, and an amino sugar is attached to the D ring through a carbon-carbon bond in addition to the usual glycoside (ether) linkage. AD-32 and rubidazole are synthetic derivatives of Adriamycin. AD-32 contains structural modifications on the amino sugar and the carbon side chain of the A ring. Rubidazole is 13-benzyloxyhydrazono adriamycin. Each of these 3 compounds has antitumor activity which is qualitatively similar in mouse systems to that of Adriamycin (11, 14, 16). Unfortunately, each compound also causes cardiotoxicity in humans or rabbits (1, 3, 5). Although potency differences may exist in the antitumor and cardiotoxic effects of these 3 structurally diverse agents, it is apparent that separation of the therapeutic and toxic activities of the anthracyclines by chemical means has not yet been achieved. Clinical development may need to be based on other considerations such as possible differences in the mechanism of action.

**ACKNOWLEDGMENTS**

The authors wish to thank Julianna C. Stewart, Thomas F. DeKonings, Roberto Garza, and Dr. Phillip I. Good for their assistance in performing these studies.

**REFERENCES**


14. Screening Data Summaries on Rubidazole (NSC-164011) and AD-32 (NSC-248131) from Mr. Robert Brennan, Automated Information Section, Development Therapeutics Program, Division of Cancer Treatment, National Cancer Institute, Bethesda, Md., April 21, 1978.


Fig. 1. a, vacuolation of degenerate myocytes, increased interstitial space, and early proliferation of fibrous connective tissue in the heart of a rabbit treated with 7-OMEN (3700 mg/sq m). Hematoxylin and phloxine-eosin, × 250; b, similar lesion in a rabbit treated with Adriamycin (250 mg/sq m). Hematoxylin and phloxine-eosin, × 250.
Chronic Cardiotoxicity Studies in Rabbits with 7-con-O-Methylnogarol, a New Anthracycline Antitumor Agent


Updated version
Access the most recent version of this article at:
http://cancerres.aacrjournals.org/content/39/12/4849

E-mail alerts
Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions
To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions
To request permission to re-use all or part of this article, contact the AACR Publications Department at permissions@aacr.org.