Metabolism and Disposition of Menogaril (NSC 269148) in the Rabbit

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ABSTRACT

We have investigated the metabolism and disposition, in rabbits, of menogaril (7-OMEN), a new anthracycline antibiotic recently introduced into clinical trials. 7-OMEN was administered by rapid i.v. injection at a dosage of 2.5 mg/kg. 7-OMEN and metabolites were assayed by high performance liquid chromatography. Plasma concentrations of 7-OMEN declined in biexponential fashion with a terminal half-life of 2.7 h. The area under the plasma concentration versus time curve was 1.3 µM x h. The systemic clearance of 7-OMEN was 57.6 ml/min/kg. No metabolite of 7-OMEN was detected in plasma. At 8 h after treatment, the cumulative urinary and biliary excretions of 7-OMEN equivalents amounted to 1.3 and 3.4% of the total administered dose, respectively. 7-OMEN was the predominant fluorescent compound in urine, but four metabolites were also seen. In bile, 7-OMEN represented only 9.6% of the cumulative excretion and six metabolites were observed. Among the organs, lungs contained the highest concentrations of parent drug. Substantial concentrations of metabolites were observed in the kidneys, liver, duodenum, and small intestine. Three of the observed metabolites of 7-OMEN have been tentatively identified as N-demethylmenogaril, 7-deoxynogarol, and N-demethyl-7-deoxynogarol.

INTRODUCTION

Anthracycline antibiotics, of which doxorubicin and daunorubicin (Chart 1) are the most important representatives, are a major class of antitumor agents. However, these two agents produce appreciable toxicity and have limited efficacy against many neoplasms. Therefore, the search continues to find anthracycline antibiotics with improved therapeutic indices (1).

7-OMEN (NSC 269148) is a semisynthetic derivative of the anthracycline antibiotic nogalamycin (Chart 1), a drug with significant experimental antitumor activity but prohibitive toxicity in animals (2). 7-OMEN has recently been introduced into Phase I clinical trials based on its broad spectrum of in vivo activity against animal tumors, its demonstrated activity after p.o. as well as i.v. administration (2, 3), and its reduced cardiotoxic potential (4). Additional interesting properties of this drug include antitumor activity in the human tumor stem cell assay (5), in vitro activity against human and hamster pancreatic adenocarcinoma cell lines (6), and a mechanism of action that might differ from that of doxorubicin (2).

Previous studies have described the plasma pharmacokinetics of 7-OMEN in beagle dogs (7) and mice (8, 9), and our laboratory has defined the organ distribution of 7-OMEN in mice (8). In these earlier studies three metabolites of 7-OMEN have been observed but only one of these, N-demethylmenogarol (Chart 1), has been identified (8, 9). In addition no previous investigation examined the urinary or biliary excretion of 7-OMEN. The present study was designed to investigate these unresolved questions.

The rabbit was selected for this study because it has been used in previous studies of the metabolism and disposition of a variety of anthracyclines, and because it is the best model for the evaluation of anthracycline-induced cardiotoxicity (10-12). In addition to describing the plasma pharmacokinetics, organ distribution, and urinary and biliary excretions of 7-OMEN in rabbits, we observed three and described the nature of two previously undescribed metabolites of 7-OMEN.

MATERIALS AND METHODS

Drug Supply and Purity

7-OMEN was supplied by the Upjohn Co. (Kalamazoo, MI) and was shown to be more than 99% pure by HPLC. HPLC analyses were performed by the method of McGovren et al. (13). Samples were analyzed on a Waters M-45 pump (Waters Associates, Milford, MA) fitted with a C8 radial pack liquid chromatography cartridge (8-mm inside diameter) (Waters Associates) held in a Z-module radial compression separation system (Waters Associates). The mobile phase consisted of 0.29 M acetic acid and 0.015 M methane sulfonic acid:acetonitrile (3:2, v/v), pumped at flow rates of 1.5-4.0 ml/min. Fluorescence was detected with an Aminco Fluoromonitor (SLM Instruments, Inc., Urbana, IL), fitted with a 470 nm excitation filter and a 500 nm cut-off emission filter. Peak areas were integrated with an Autolab system IV computer (Spectra-Physics, Autolab Division, Santa Clara, CA). All concentrations were expressed in 7-OMEN equivalents based on standard curves prepared in the appropriate biological matrix.

Chemicals and Reagents

Methane sulfonic acid was obtained from Aldrich Chemical Co., Inc. (Milwaukee, WI). Xanthine and xanthine oxidase (from buttermilk) were purchased from Sigma Chemical Co. (St. Louis, MO). 7-Con-O-ethylno- garol, 7-deoxynogarol, norgarol, nogarene, and N-demethylmenogarol were kindly provided by Dr. J. P. McGovren of the Upjohn Co. All other chemicals were reagent grade. N-Demethyl-7-deoxynogarol was produced by incubating N-demethylmenogarol with xanthine oxidase, an enzyme known to convert anthracycline antibiotics to 7-deoxycglycines (14). The conditions utilized in this reaction are described below.

Animals

Male New Zealand White rabbits, weighing 1.9-2.9 kg, were obtained from Charles River Breeding Laboratories, Inc. (Wilmington, MA). They were housed in separate cages in a controlled environment with 12-h light and dark cycles and were fed a standard chow diet (Ralston Purina Co., St. Louis, MO) with water ad libitum.
**In Vivo Studies**

**Surgical Preparations.** Four groups of three rabbits each were studied. Groups A and D were treated without surgical preparation. Cannulations of the femoral vein (groups B and C) and of the bladder and common bile duct (group C) were accomplished under general anesthesia (11). Anesthesia was induced with pentobarbital (35 mg/kg i.v. via ear vein) or with a combination of ketamine (200 mg i.m.) and pentobarbital (20 mg/kg i.v. via ear vein). Anesthesia was maintained with diethyl ether. After free flows of bile and urine were assured, ether administration was discontinued and the animal was allowed to regain consciousness.

**Treatment and Sample Collection.** Rabbits received 7-OMEN dissolved in 0.01 M glucuronic acid as an i.v. bolus injection via ear vein at a dosage of 2.5 mg/kg and in a volume of 1.9 to 2.9 ml. Group A rabbits were killed by an overdose of pentobarbital 1 min after treatment. Brains, hearts, lungs, livers, kidneys, duodena, pancreata, small intestines, and skeletal muscle (thigh) were quickly dissected, weighed, frozen on dry ice, and stored at -20°C until analysis. For group B rabbits, 1 ml heparinized (50 units/ml) blood samples were obtained from the femoral catheter at 1, 3, 5, 10, 15, 30, 45, and 60 min after treatment. Animals were then killed, and their organs were obtained and processed as described for group A. For group C rabbits, 1 ml heparinized (50 units/ml) blood samples were obtained from the femoral catheter at 0.25, 0.50, 0.75, 1, 2, 4, 6, and 8 h after treatment. Urine and bile were collected from 0 to 0.25, 0.25 to 0.50, 0.50 to 1, 1 to 2, 2 to 4, 4 to 6, and 6 to 8 h after treatment. The animals were killed 8 h after treatment and their organs were obtained and processed as described for group A. For group D rabbits, 1 ml heparinized (50 units/ml) blood samples were obtained from the ear vein contralateral to the injection at 13, 16, 20, and 24 h after treatment. The animals were then killed and their organs were obtained and processed as described for group A. Blood for all animals and urine and bile for group C were also obtained prior to and after injection of 7-OMEN. Blood samples were immediately centrifuged at 12,200 × g for 2 min, and the resulting plasma supernatant was collected. Plasma, urine, and bile samples were stored at -20°C until analysis.

**Sample Analyses.** Plasma samples were analyzed by a modification of the method of McGovren et al. (13). Samples (0.25-0.40 ml) were deproteinized with 0.05-0.08 ml of 0.05 M glucuronic acid and 0.80-0.96 ml of acetonitrile:methanol (1:1, v/v), containing 0.25-1 μM 7-con-0-ethynogarol, were added to 1- to 2-ml aliquots of the homogenate. The mixture was centrifuged at 27,000 × g for 10 min at 4°C. The supernatant fraction was transferred to prechilled, screw-cap vials, shielded from light, and stored at 4°C until injection onto the HPLC column. The lowest limit of detection of 7-OMEN in organs was approximately 0.1 nmol/g.

One control rabbit was killed without having received 7-OMEN, and its organs were processed as were those of other rabbits. The HPLC chromatograms obtained from the organs of this rabbit did not show any peak that would interfere with the measurement of 7-OMEN or its metabolites.

**Pharmacokinetic Studies.**

A computer simulation of the decline in plasma concentrations of 7-OMEN was performed on the MLLAB program (15) (Division of Computer Resources and Technology, NIH, Bethesda, MD). Pharmacokinetic parameters were derived from the modeled data according to the method of Gibaldi and Perrier (16). The area under the plasma concentration versus time curve was calculated with the trapezoidal rule by integration, until infinity, of the modeled concentration-time data. The total body clearance was obtained by dividing the dose by the area under the plasma concentration versus time curve.

**Metabolite identification**

Metabolites were tentatively identified by cochromatography on HPLC and TLC with known standards of 7-OMEN, N-demethylmenogaril, 7-deoxyxynogarol, nogarol, nogarene, and the previously mentioned reaction product of N-demethylmenogaril and xanthine oxidase. Cochromatographs were also performed with the products of the in vitro studies described below. TLC analyses utilized Silica Gel 60 TLC plates (E. Merck, Darmstadt, West Germany) that were developed in an ascending fashion in chloroform:methanol:acetic acid:water (80:20:14:6, v/v), for 16 cm. Fluorescent spots were identified under 254 nm light (UVS-54 Mineralight, Ultraviolet Products, San Gabriel, CA).

**In Vitro Studies.**

Reaction mixtures (total volume, 10 ml) for in vitro studies contained 40 mM potassium phosphate (pH 7.4), 1 mM xanthine, xanthine oxidase (protein concentration, 0.48 mg/ml), and 1.54 mM magnesium sulfate. All reactions were started by the addition of 7-OMEN or N-demethylmenogaril to a final concentration of 5 μM and were performed at 37°C in a Dubnoff metabolic shaker (120 oscillations/min) under anaerobic conditions produced by a continuous flow of nitrogen. At appropriate times duplicate 0.5-ml samples were obtained, and were deproteinized with 0.5 ml of 0.01 M glucuronic acid and 2 ml of acetonitrile:methanol (1:1, v/v), containing 1 μM 7-con-0-ethynogarol. Following centrifugation at 27,000 × g for 10 min, the supernatant fractions were collected and injected onto the HPLC column.

**RESULTS**

**In Vivo Studies.**

Plasma. Although there was some suggestion of nonlinear kinetics in the decay of plasma concentrations of 7-OMEN (Chart 2), the half-saturating value (Michaelis constant) was more than 100 times the peak plasma concentration. Thus linear kinetic models were used. Following a peak concentration of 1.22 ± 0.11 (SD) μM at 1 min after injection, 7-OMEN disappeared from plasma according to the biexponential equation:

\[
C = 1.74e^{-0.21t} + 0.34e^{-0.29t}
\]
MENOGARIL IN RABBITS

Chart 2. Plasma concentrations of parent drug in rabbits treated with 7-OMEN. Nine rabbits received 7-OMEN by rapid i.v. injection at a dosage of 2.5 mg/kg. Plasma was obtained at various times after treatment. 7-OMEN was assayed by HPLC. Points, means of 3-7 determinations; bars, SD. The curve has been obtained by fitting the plasma concentrations of 7-OMEN to a biexponential equation.

\[
C(t) = C_0 e^{-t/\tau_1} + (C_0 - C_{\infty}) e^{-t/\tau_2}
\]

where \( C \) is the concentration of 7-OMEN in \( \mu M \) and \( t \) is the time in h. The elimination half-life was 2.66 h and the apparent volume of the central compartment was 2.22 liter/kg or 5.25 liter for a rabbit of average weight. The area under the plasma concentration versus time curve from 0 until infinity was 1.34 \( \mu M \times h \), and the total body clearance was 57.6 ml/min/kg or 136.3 ml/min for a rabbit of average weight. No metabolite of 7-OMEN was detected in plasma.

Urine. The cumulative urinary excretion of 7-OMEN equivalents increased almost linearly with time (Chart 3). By 8 h after treatment cumulative urinary excretion accounted for 1.3 ± 0.2% of the total administered dose. Except for a slightly higher rate of excretion during the first 15 min after treatment, the rate of excretion was fairly stable at approximately 10 \( \mu g \) of 7-OMEN equivalents/h (Chart 3). 7-OMEN remained the predominant urinary compound at all times (Chart 4). However, the percentage of urinary drug due to 7-OMEN decreased progressively while increasing amounts of metabolites were excreted. Four metabolites were observed in the urine (Table 1). One of these was tentatively identified as N-demethylmenogaril (Chart 1), but the three other metabolites (R4, R5, and R6) are unidentified. Their retention times in HPLC are listed in Table 2.

Bile. The cumulative biliary excretion of 7-OMEN equivalents increased progressively with time (Chart 3). By 8 h after treatment the cumulative biliary excretion accounted for 3.4 ± 1.2% of the total administered dose. The rate of biliary excretion of...
drug was not as stable as was that of urinary excretion. It increased to reach a maximum of 40 ng/h during the time interval of 1–2 h after treatment and, thereafter, decreased progressively (Chart 3). 7-OMEN was the major fluorescent compound in bile only during the first 15 min after treatment (Chart 5) and represented more than 80% of the total 7-OMEN excretion of drug (Table 1). Six metabolites were observed in bile (Table 1). Three of these were tentatively identified by cochromatography as N-demethylmenogaril, 7-deoxynogarol, and N-demethyl-7-deoxynogarol (Chart 1). N-Demethylenogaril represented more than 20% of the total 7-OMEN fluorescent equivalents detected chromatographically in bile during all time intervals. The percentage of biliary drug due to metabolite R4 increased progressively and, over the entire 8-h period, the amount of metabolite R4 exceeded that of any other drug form. Metabolite R5 was the major biliary compound between 0.5 and 2 h after treatment. Metabolites designated as 7-deoxynogarol, N-demethyl-7-deoxynogarol, and metabolite R6 were quantitatively less important but were still easily detectable in the bile.

**Organs.** The lungs contained the highest concentrations of 7-OMEN at all times (Table 3). Heart also contained high initial concentrations of 7-OMEN (17.2 ± 18.2 nmol/g at 1 min after injection). In spleen concentrations of 7-OMEN were initially less than 1 nmol/g but increased to 5.3 ± 0.7 and 3.9 ± 3.4 nmol/g at 1 and 8 h after treatment, respectively. This resulted in an area under the concentration versus time curve of 66.7 ± 23.3 nmol/g x h, a value exceeded only by that for the lungs. Other organs contained small or negligible concentrations of 7-OMEN.

<table>
<thead>
<tr>
<th>Organ</th>
<th>1 min</th>
<th>8 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lungs</td>
<td>51.5 ± 13.0a</td>
<td>141.6 ± 51.9</td>
</tr>
<tr>
<td>Heart</td>
<td>17.2 ± 18.2</td>
<td>25.1 ± 8.1</td>
</tr>
<tr>
<td>Pancreas</td>
<td>1.1 ± 0.7</td>
<td>15.0 ± 9.5</td>
</tr>
<tr>
<td>Skeletal muscle</td>
<td>0.6 ± 0.4</td>
<td>5.2 ± 2.6</td>
</tr>
<tr>
<td>Spleen</td>
<td>0.4 ± 0.3</td>
<td>66.7 ± 41.4</td>
</tr>
<tr>
<td>Duodenum</td>
<td>0.3 ± 0.2</td>
<td>2.5 ± 1.2</td>
</tr>
<tr>
<td>Liver</td>
<td>0.3 ± 0.3</td>
<td>2.9 ± 0.4</td>
</tr>
<tr>
<td>Small intestine</td>
<td>0.3 ± 0.2</td>
<td>5.2 ± 4.4</td>
</tr>
<tr>
<td>Kidney</td>
<td>0.2 ± 0.4</td>
<td>17.6 ± 23.3</td>
</tr>
<tr>
<td>Brain</td>
<td>0.1 ± 0.1</td>
<td>1.3 ± 1.4</td>
</tr>
</tbody>
</table>

At 24 h after treatment concentrations of 7-OMEN were less than 0.1 nmol/g in all organs. 7-OMEN represented more than 80% of the total 7-OMEN fluorescence equivalents at all times in all organs except liver, duodenum, small intestine, and kidney, where one to three metabolites were observed (Table 4). However, the concentrations of metabolites never exceeded 1 nmol/g in any organ. Three metabolites of 7-OMEN were observed in tissue and were tentatively identified by cochromatography. In liver a compound appearing to be 7-deoxynogarol was the predominant compound. The area under the concentration versus time curve for this compound was 13.9 ± 4.1 nmol/g x h, a value 5 times higher than that for 7-OMEN.
methy-7-deoxynogarol were quantitatively less important, with areas under the concentration versus time curve of 4.9 ± 5.5 and 0.8 ± 0.8 nmol/g x h, respectively. In kidney 7-deoxynogarol was also the major metabolite. The area under the renal concentration versus time curve for this compound was 11.9 ± 4.3 nmol/g x h, or 52.8 ± 34.6% of the area under the curve of total renal 7-OMEN fluorescence equivalents versus time. Substantial renal concentrations of N-demethylmenogaril were also measured and the area under the renal concentration versus time curve for this metabolite was 4.3 ± 6.5 nmol/g x h. 7-Deoxynogarol was the only significant metabolite in small intestine and duodenum, with areas under the concentration versus time curve of 7.7 ± 6.0 and 4.4 ± 3.3 nmol/g x h, respectively. These values represent 52.8 ± 34.6 and 54.9 ± 28.6% of the area under the curve of total drug fluorescence versus time, respectively. Materials felt to be N-demethylmenogaril, 7-deoxynogarol, and/or N-demethyl-7-deoxynogarol were observed in other organs, but in much smaller concentrations than those of 7-OMEN.

**In Vitro Studies**

In the presence of xanthine oxidase and under anaerobic conditions 7-OMEN was extensively converted to a metabolite that had the same HPLC characteristics as did 7-deoxynogarol. After 30 min of incubation, this metabolite represented 81.6 ± 6.0% of the total 7-OMEN fluorescence equivalents. Of note, this conversion was accompanied by a decrease in total 7-OMEN fluorescence equivalents from 5.1 ± 0.7 to 2.9 ± 0.8 µM (P < 0.025, Student's paired t test).

Under similar conditions N-demethylmenogaril was metabolized extensively to the corresponding 7-deoxy derivative, N-demethyl-7-deoxynogarol. After 60 min of incubation, N-demethyl-7-deoxynogarol represented 81.1 ± 9.5% of the total 7-OMEN fluorescence equivalents. This conversion was also accompanied by a decrease in total 7-OMEN fluorescence equivalents from 2.7 ± 0.4 to 1.6 ± 0.3 µM (P < 0.02, Student's paired t test).

**DISCUSSION**

In this study 7-OMEN disappeared from plasma of rabbits more rapidly than it did from plasma of mice, where a terminal half-life of 10 to 12 h has been observed (8, 9). As might be expected in view of this, the total body clearance of 0.78 liter/min/m² calculated for the rabbit is greater than the values of 0.09 to 0.24 liter/min/m² calculated for mice. In contrast, the plasma pharmacokinetic parameters of 7-OMEN in the rabbit are similar to those reported for the beagle dog, i.e., a terminal half-life of 3.3 h and a total body clearance of 0.87 liter/min/m² (7). At present it is not clear how these pharmacokinetic parameters could be used to predict the pharmacokinetic behavior of 7-OMEN in human beings, but ongoing clinical pharmacokinetic studies should provide data to allow meaningful comparisons.

The biliary excretion of 7-OMEN and metabolites by the rabbit was limited, with less than 1.5% of the administered dose recovered in the first 8 h after treatment. This value is in the range of those reported for rabbit studies with other anthracyclines, including doxorubicin and daunorubicin (10–12). Since the urinary excretion of other anthracycline antibiotics by humans is 5–15% of the administered dose over several days (17–19), it is not likely that urine will be a major route of elimination of 7-OMEN in humans.

The biliary excretion of 7-OMEN and metabolites by the rabbit was also limited, with 3.4% of the administered dose recovered in bile during the first 8 h after treatment. This value is much lower than that reported for doxorubicin and daunorubicin (10). While 7-OMEN was the predominant fluorescent compound in urine, concentrations of 7-OMEN in bile were rapidly exceeded by those of several metabolites. Three of the six biliary metabolites have been tentatively identified as N-demethylmenogaril, 7-deoxynogarol, and 7-demethyl-7-deoxynogarol. The three other metabolites are presently unidentified. Two of these (R4 and R6) have short retention times, consistent with polar conjugates. Alternatively, N-demethylation appeared to be associated with decreased retention times and therefore R4 and R6 could represent N,N-dimethyl derivatives of 7-OMEN or metabolites. The retention time of metabolite R5 was longer than that of 7-OMEN. This metabolite could be a conjugate or an N-demethyl derivative of nogarene, a compound that is not eluted from the column in our HPLC conditions.

The organ distributions of 7-OMEN in mice and rabbits are comparable (8) and resemble those described for some other anthracyclines (11, 12), but not those of doxorubicin and daunorubicin (10). A number of anthracycline antibiotics, including 7-OMEN, are highly concentrated in the lungs, whereas the greatest concentrations of doxorubicin and daunorubicin are observed in the kidneys and liver (11, 12, 19–23). The mechanism of this pulmonary sequestration and the clinical relevance of these differential organ distribution patterns remain to be established. It is possible that the lungs serve as a reservoir from which the drug is slowly released and distributed to the other organs. In both mouse and rabbit there were increases in splenic 7-OMEN concentrations from 1 min to 8 h after injection. Since the weight of the organ did not change significantly between these two time points, these increases in splenic concentrations reflect a true accumulation of drug. No 7-OMEN was detected in brain.

Organs contained three metabolites of 7-OMEN that were tentatively identified as N-demethylmenogaril, 7-deoxynogarol, and 7-demethyl-7-deoxynogarol. 7-Deoxynogarol was a major metabolite in liver, kidneys, and the gastrointestinal tract. In these organs the exposure to 7-deoxynogarol, as measured by the area under the concentration versus time curve, was more important than that to 7-OMEN itself. Since N-demethylmenogaril has been shown cytotoxic, albeit less so than is 7-OMEN (9),...
these metabolites may play a role in the therapeutic activity or toxicity of the drug. In addition the presence of 7-deoxynogarol in the organs and bile indicates that 7-OMEN is a substrate for reductive cleavage of the ether bond at carbon 7. It is likely that this pathway involves the formation of free radical intermediates that have been implicated in the activity and toxicity of other anthracycline antibiotics (17, 23, 24).

Taking into account the weight of the organs and extracellular fluid, their concentrations of 7-OMEN and metabolites at 8 h after treatment, and the cumulative urinary and biliary excretions through that time, we calculated a recovery of approximately 10% of the total administered dose. We do not believe that high concentrations of 7-OMEN and metabolites would be measured in the organs that were not sampled in this study, such as fat, bone, and skin. It is more likely that some metabolites have not been detected by the technique used in this study. Nogarene, which has the structure of a bisanhydroaglycone, was not eluted from the column. Bisanhydroaglycones have been observed in plasma, urine, and tissues of animals and human beings treated with other anthracycline antibiotics (25-27), and therefore nogarene could be one of the undetected metabolites of 7-OMEN. However, TLC analysis of tissue, bile, and urine samples did not indicate the presence of nogarene. Also the formation of less or nonfluorescent metabolites must be considered. The apparent conversion of 7-OMEN and N-demethylnogaril to their 7-deoxy derivatives was accompanied by a decrease of total fluorescence. This might be due to a lower fluorescence efficiency of reaction products or to the formation of unrecognized nonfluorescent compounds. Our laboratory has demonstrated that xanthine oxidase and rat liver fractions induce a true loss of fluorescence with the anthracycline antibiotic, marcellomycin (14). A similar phenomenon could happen with 7-OMEN.

The pharmacology of 7-OMEN has now been characterized in several animal species. The differences in pharmacological behavior among these species need to be interpreted in light of the results of the ongoing clinical studies. The animal investigations have demonstrated that the metabolism of 7-OMEN is likely to follow two major pathways: N-demethylation and reductive cleavage at position 7. However, the low recovery of drug and metabolites in bile, urine, and tissues and our in vitro data suggest the formation of nonfluorescent metabolites, a possibility currently under investigation.

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