Human Pharmacokinetics, Excretion, and Metabolism of the Anthracycline Antibiotic Menogaril (7-OMEN, NSC 269148) and Their Correlation with Clinical Toxicities

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ABSTRACT

In a Phase I study, menogaril (7-OMEN) was administered daily for 5 days/course, every 21-28 days. Doses of 3.5, 7, 11.5, 17, and 31.5 mg/m² were infused over 1 h, and doses of 42, 50, and 56 mg/m² were infused over 2 h. Pharmacokinetics was studied at all dosages. Plasma and urine samples were collected from 24 patients, and bile samples were also collected from 2 patients. 7-OMEN and metabolites were measured by high-performance liquid chromatography. 7-OMEN was the major plasma fluorescent species at all times, with only trace amounts of N-demethyl menogaril observed. 7-OMEN disappeared from plasma biexponentially with t½ values of 0.19 ± 0.04 (mean ± SE) h and 13.22 ± 1.54 h. Plasma pharmacokinetics of 7-OMEN was linear from 3.5-56 mg/m², area under the curve increased proportionally with dosage. Total body clearance of 7-OMEN was 28.18 ± 3.33 liter/m²/h, Vc was 224 ± 30.8 liter/m², and Vss was 370 ± 25.7 liter/m². Plasma pharmacokinetics of 7-OMEN studied on multiple days of a given course were similar. Urinary excretion of 7-OMEN and fluorescent metabolites accounted for 5.4 ± 0.4% of the daily dose. Parent compound still represented ≥80% of urinary drug fluorescence after 24 h. N-demethyl menogaril was the only other fluorescent drug species detected in urine. In two patients with biliary tract drains, biliary excretion of drug fluorescence accounted for 2.2-4.2% of the daily dose. Only 7-OMEN and N-demethyl menogaril were detected in bile by high performance liquid chromatography and thin layer chromatography. 7-OMEN was the major fluorescent biliary species, but, by 24 h, N-demethyl menogaril accounted for approximately 40% of biliary drug fluorescence. When considered in light of each patient’s observed toxicities, excellent relationships were observed between the plasma area under the curve of 7-OMEN and the percentage of decreases in WBC and absolute neutrophil count. These latter findings should be useful in developing more precise and intelligent dosing schemes for 7-OMEN.

INTRODUCTION

Anthracycline antibiotics, which doxorubicin and daunorubicin (Fig. 1) are the most important representatives, are a major class of antitumor agents. However, these two agents produce considerable toxicity and have limited efficacy against many neoplasms. Therefore, the search continues for anthracycline antibiotics with improved therapeutic indices, altered spectra, or activity of both (1).

7-OMEN is a semisynthetic derivative of the anthracycline antibiotic nogalamycin (Fig. 1), a drug with significant experimental antitumor activity but prohibitive toxicity in animals (2). 7-OMEN has 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).

The mechanism of action of 7-OMEN may differ from that of doxorubicin. 7-OMEN is most toxic to cells in G1 phase, whereas doxorubicin is most toxic to cells in S phase (2). In addition, while doxorubicin interacts strongly with DNA, 7-OMEN interacts only weakly with DNA and is highly cytotoxic at concentrations which do not inhibit nucleic acid synthesis (2, 5). Finally, when various tumor lines are incubated in vitro with 7-OMEN or doxorubicin, 7-OMEN fluorescence is localized mainly in the cytoplasm, whereas doxorubicin fluorescence accumulates primarily in the nucleus (2, 6).

ABSTRACT

Patient Selection. All patients entering this trial had to fulfill the following criteria: histological proof of malignant disease which had failed conventional chemotherapy or for which no conventional therapy existed, recovery from all toxicities from prior treatments and passage of at least 4 weeks from any prior chemotherapy or radiotherapy, a minimal life

Received 6/27/85; revised 11/8/85; accepted 11/11/85.

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The abbreviations used are: 7-OMEN, menogaril; HPLC, high performance liquid chromatography; TLC, thin layer chromatography; AUC, area under the curve of plasma drug concentration versus time; Vc, volume of the central compartment; Vss, steady-state volume of distribution.

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1This work was supported in part by Contract NO1CM27541, and Grant IP50CA32107 awarded by the National Cancer Institute, Department of Health and Human Services, Bethesda, MD 20205.

2To whom requests for reprints should be addressed.
expectancy of 12 weeks, a Karnofsky performance status ≥50%, ade-
quate bone marrow function (WBC >3,500 cells/µl), and platelet count
≥100,000/µl, adequate liver function (bilirubin ≤2.0 mg/100 ml, and
adequate renal function (creatinine ≤2.0 mg/100 ml, and a 24-h creatinine
clearance of ≥50 ml/min). Previous anthracycline administration did not,
by itself, exclude patients from this study; however, all patients must
have had an ejection fraction, as assessed by MUGA scan, ≥45% at
rest. Objective measurable disease was desirable, but not required.
Written informed consent in accordance with Federal and institutional
policies was obtained from all patients prior to their entry onto study.
Before entry onto study, each patient had a detailed history taken and
a physical examination performed. Tumor measurements were made
and performance status was assessed. Laboratory studies relevant to
this paper included pretreatment and weekly complete and differential
blood counts and platelet counts.

**Sample Acquisition.** Heparinized blood samples were obtained before
and at multiple times during and after the 7-OMEN infusion. Specifically,
on day 1 of the 5-day course, blood was obtained prior to and at 0.5-h
intervals during the 7-OMEN infusion. In addition, samples were obtained
at 5, 10, 20, 30, and 60 min, and at 2, 4, 6, 12, 18, and 24 h after
cessation of the infusion. Blood samples were also obtained before the
7-OMEN infusion on days 2, 3, 4, and 5 of each course. In some patients,
a repeat of the intensive sampling scheme performed on day 1 was also
performed on day 4 or 5 of a course to investigate whether the phar-
cokinetics on later days of a course were similar to that on the first
day. Blood samples were immediately centrifuged at 1000 × g for 10
min, and the resulting plasma supernatant was immediately removed
and frozen at −20°C until analyzed. During the first 24 h after drug
administration, urine was collected as voided and stored as 4-h aliquots
in opaque containers at 4°C. Subsequently, a portion of each 4-h
collection was frozen and stored at −20°C until analyzed.

Two of the patients on this study had indwelling biliary tract drains
and provided the opportunity to collect and analyze the biliary excretion
of 7-OMEN and its metabolites. The first of these patients had completely
normal serum liver function tests (bilirubin, 0.8 mg/dl; aspartate aminotransferase,
35 units/liter; alanine aminotransferase, 7 units/liter; lactate
dehydrogenase, 136 units/liter; alkaline phosphatase, 292 units/liter;
total protein, 6.9 g/dl; and albumin, 4.2 g/dl). The second patient had
moderate hepatic dysfunction as assessed by serum liver function tests
(bilirubin, 5.4 mg/dl; aspartate aminotransferase, 56 units/liter; alanine
aminotransferase, 36 units/liter; lactate dehydrogenase, 143 units/liter,
alanine phosphatase, 1,102 units/liter, protein, 6.2 g/dl, and albumin, 2.9
g/dl). Each patient had bile collected on ice and stored frozen as 4-h
aliquots during the first 24 h after initiation of 7-OMEN therapy.
The second of these patients also had the subsequent 4 days of biliary
excretion collected and stored frozen as 24-h aliquots.

**RESULTS**

At all dosages, plasma concentrations of 7-OMEN rose pro-
gressively during the drug infusion, after which they decayed in
biexponential fashion with t1/2 of 0.19 ± 0.04 h (mean ± SE) and
t2/3 of 13.22 ± 1.54 h (Fig. 2; Table 1). The pharmacokinetics of
7-OMEN was linear over the dosage range studied, the AUC
increasing linearly with increased dosage (Fig. 3; Table 1). As
can be inferred from this, the total body clearance of 7-OMEN,
28.18 ± 3.33 liter/h/m2, was not altered by increasing the dose
(Table 1). Similarly, neither the volume of the central compart-
ment, 370 ± 30.8 liter/m2, nor the steady-state volume of distribu-
tion, 370 ± 25.7 liter/m2, were altered by increasing the amount
of drug infused. These plasma pharmacokinetic parameter values did not change with repeated dosing since those
determined on day 4 or 5 of a course were unchanged from
those observed in that same patient on day 1.

At all times, 7-OMEN was the major fluorescent species pres-
7-OMEN PHARMACOKINETICS AND TOXICITIES

Fig. 2. Concentrations of 7-OMEN in plasma of patients treated with varying dosages of 7-OMEN. Dosages of 3.5 to 31.5 mg/m² (A) were infused over 1 h while dosages of 42 to 56 mg/m² (B) were infused over 2 h. Concentrations of 7-OMEN were determined by HPLC, as described in "Materials and Methods." Points, mean values. The number of courses studied at each dosage are indicated in parentheses next to the dosage.

ent in plasma. Although small HPLC peaks corresponding to the mono- and didemethyl metabolites of menogaril were observed, the plasma concentrations of these materials were negligible and represented ≤5% of plasma drug fluorescence at any time.

Urinary excretion of 7-OMEN and its metabolites increased progressively over the 24 h after drug injection, and accounted for approximately 5% of the administered dose (Fig. 4). Only two fluorescent drug species were observed in urine (Fig. 5). Of these, 7-OMEN was easily the major species, still accounting for greater than 70% of drug fluorescence at 24 h after drug administration. The remainder of drug fluorescence was accounted for by N-demethyl menogaril. Although the proportion of total fluorescence in urine due to this metabolite increased with time, it never represented more than 20 to 30% of urinary drug fluorescence (Fig. 5). There were no measurable amounts of didemethyl menogaril or any aglycons in the urine at any time during the 24 h period of study.

As the urinary excretion, biliary excretion of 7-OMEN and metabolites increased progressively in the two patients studied (Fig. 6). In the first patient, the 24-h biliary excretion accounted for 4.2% of the dose of drug administered on day 1 of the 5-day course. In the second patient, this value was 1.9%. Not only was there reasonable agreement between these two patients, but there was also internal consistency for the second patient, since the percentage of daily dose of 7-OMEN excreted in the bile on days 2, 3, 4, and 5 was 2.2, 1.1, 2.7, and 1.3%, respectively. Only two fluorescent species were present in the bile (Fig. 7). In both patients, 7-OMEN was the major biliary fluorescent drug species. However, the percentage of drug fluorescence accounted for by N-demethyl menogaril increased progressively, so that from 16 to 24 h, parent compound and its N-demethyl metabolite were present in bile at ratios of approximately 6:4, respectively. In addition to analysis by HPLC all bile samples were analyzed by TLC. This was to confirm the presence of the two drug forms in the bile and to rule out the presence of very nonpolar drug forms, such as aglycons, which might not elute from the HPLC column, or very polar drug forms, such as conjugates, which might elute with the solvent front and thereby escape detection. Only two fluorescent drug spots, corresponding to 7-OMEN and N-demethyl menogaril, were observed. There were no other fluorescent metabolites observed on the TLC plate, at the origin, or at the solvent front.

In addition to defining the pharmacokinetic behavior of 7-OMEN in humans, the availability of toxicity data from our Phase I study allowed us to attempt relating the pharmacokinetics and pharmacodynamics of this agent. It was apparent that analyses using peak plasma concentrations were of no use. Similarly, analyses using dosage and change in WBC were suboptimal. The first of these variables neglected interpatient variability with regard to drug disposition, and the latter neglected the fact that individual patients were treated with pretreatment WBC of 3,500 to 18,500/μl, which by definition put a limit on the maximum change in WBC that could occur. On the other hand, an excellent relationship was obtained when area under the curve of 7-OMEN plasma concentration versus time was related to the percentage of decrease in WBC, i.e.,

\[
\text{Pretreatment WBC} - \text{nadir WBC} \times 100 \\
\text{Pretreatment WBC}
\]

(Figs. 8 and 9). This relationship was well described by two different models.

The first of these, taking a form similar to that of a one compartment model approaching steady state during continuous infusion, was described by the equation:

\[
\% \text{ of decrease in WBC} = 100 \left(1 - e^{-0.087 \text{ AUC}}\right)
\]

(Fig. 8). When this relationship was evaluated by comparing the
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Table 1

<table>
<thead>
<tr>
<th>Dosage (mg/m²)</th>
<th>Dosage (μmol/m²)</th>
<th>No. of studies</th>
<th>α (h⁻¹)</th>
<th>bₐ (h⁻¹)</th>
<th>bₐb (h⁻¹)</th>
<th>AUC (μM·h)</th>
<th>Total body clearance (liter/h/m²)</th>
<th>V₁ (liter/m²)</th>
<th>V₀ (liter/m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.5</td>
<td>6.3</td>
<td>2</td>
<td>12.08 ± 4.2</td>
<td>0.08 ± 0.22</td>
<td>0.24 ± 0.22</td>
<td>13.2 ± 11.6</td>
<td>0.158 ± 0.084</td>
<td>57.7 ± 30.4</td>
<td>135 ± 50</td>
</tr>
<tr>
<td>7</td>
<td>12.95</td>
<td>3</td>
<td>7.06 ± 3.69</td>
<td>0.17 ± 0.08</td>
<td>0.113 ± 0.06</td>
<td>11.4 ± 5.9</td>
<td>0.95 ± 0.33</td>
<td>18.0 ± 6.9</td>
<td>174 ± 24</td>
</tr>
<tr>
<td>11.5</td>
<td>21.275</td>
<td>3</td>
<td>11.09 ± 4.13</td>
<td>0.08 ± 0.02</td>
<td>0.093 ± 0.016</td>
<td>8.0 ± 1.5</td>
<td>0.79 ± 0.18</td>
<td>28.4 ± 6.4</td>
<td>123 ± 17</td>
</tr>
<tr>
<td>17.5</td>
<td>32.375</td>
<td>1</td>
<td>7.36</td>
<td>0.09</td>
<td>0.121</td>
<td>5.7</td>
<td>0.813</td>
<td>39.9</td>
<td>98</td>
</tr>
<tr>
<td>31.5</td>
<td>58.275</td>
<td>2</td>
<td>11.12 ± 2.24</td>
<td>0.06 ± 0.01</td>
<td>0.075 ± 0.004</td>
<td>9.3 ± 0.5</td>
<td>1.95 ± 0.26</td>
<td>30.4 ± 4.0</td>
<td>100 ± 33</td>
</tr>
<tr>
<td>42</td>
<td>77.7</td>
<td>5</td>
<td>6.32 ± 1.97</td>
<td>0.20 ± 0.09</td>
<td>0.057 ± 0.006</td>
<td>12.7 ± 1.2</td>
<td>3.46 ± 0.67</td>
<td>25.5 ± 4.1</td>
<td>212 ± 13</td>
</tr>
<tr>
<td>50</td>
<td>91.7</td>
<td>4</td>
<td>3.66 ± 1.40</td>
<td>0.33 ± 0.19</td>
<td>0.057 ± 0.016</td>
<td>16.2 ± 5.2</td>
<td>6.16 ± 2.07</td>
<td>22.4 ± 8.0</td>
<td>362 ± 48</td>
</tr>
<tr>
<td>56</td>
<td>103.6</td>
<td>4</td>
<td>4.84 ± 2.52</td>
<td>0.32 ± 0.13</td>
<td>0.049 ± 0.012</td>
<td>17.2 ± 4.3</td>
<td>4.8 ± 1.01</td>
<td>26.3 ± 6.0</td>
<td>355 ± 126</td>
</tr>
</tbody>
</table>

Mean | 7.48 | 0.19 | 0.071 | 13.22 | 26.18 | 224 | 370 |
SD   | 5.20 | 0.20 | 0.04 | 7.39 | 16.30 | 148 | 126 |
SE   | 1.06 | 0.04 | 0.01 | 1.54 | 3.33 | 30.80 | 25.70 |

Fig. 3. Relationship of dosage to area under the curve of plasma concentration of 7-OMEN versus time. A, data on individual patients and courses of therapy. B, means ± SD of all courses studied at each dosage.

Fig. 4. Urinary excretion of 7-OMEN and metabolites by patients treated with 7-OMEN. Points, means ± SD of 24 courses.

The other relationship which fit our data was the Hill equation (14) which produced the equation:

\[
\text{% of decrease in WBC} = \frac{(100) (\text{AUC}^{1.43})}{(10.14)^{1.43} + (\text{AUC})^{1.43}}
\]

(Fig. 8). In this case, percentage of decrease in WBC equals the effect measured, 100 represents the maximum effect possible, 10.14 represents the AUC that produces 50% of the maximum effect, and 1.63 is a constant derived from our set of data. When this relationship was evaluated by comparing the predicted percentage of decrease in WBC with that actually observed (Fig. 9), the data were very similar to those produced by the previous model, i.e., it was close to the line of identity with an r value of 0.893. There was no statistical difference between the two models with regard to their suitability in describing the data (15).

When we applied the same two models to the relationship of area under the curve and the percentage of decrease in absolute neutrophil count, we observed results very similar to those seen with total WBC (Figs. 10 and 11). Once again, each model produced an excellent description of the data, with the second model producing a slightly, but not statistically significantly,
DISCUSSION

The introduction of 7-OMEN into clinical trials represents another attempt to find an anthracycline antitumor antibiotic with true advantages over doxorubicin and daunorubicin, the most commonly used members of this major class of antineoplastic drugs. When considered in light of previous animal and clinical studies of doxorubicin and daunorubicin, as well as animal studies of 7-OMEN, the data presented in this manuscript may provide a better appreciation of the effects of species and structural differences on anthracycline metabolism and disposition. In addition, the clinical pharmacological data and the data correlating the pharmacokinetics and pharmacodynamics of 7-OMEN should provide a foundation for more intelligent use of this drug in subsequent Phase II and Phase III clinical trials.

The major metabolic alteration of 7-OMEN by humans involves demethylation of the tertiary amino sugar attached to the D ring of the anthracycline nucleus. This is in contrast to the biotransformation of doxorubicin and daunorubicin by humans and animals, where cytoplasmic NADPH-requiring aldo-keto reductase reduces the carbonyl function attached to the A anthracycline ring to produce the glycosides doxorubicinol and daunorubicinol (16–22). Moreover, with time these reduced glycosidic metabolites of doxorubicin and daunorubicin appear in plasma at concentrations that approach or exceed those of the parent compound. In contrast there is a very small percentage of drug present in plasma as 7-OMEN metabolites. Our data on the fluorescent drug species present in plasma of humans treated with 7-OMEN are similar to those in our previously published studies of 7-OMEN metabolism and disposition in rabbits (8) and mice (9). More precisely, we observed no plasma fluorescent drug species other than 7-OMEN in rabbit plasma (8), but did detect measurable concentrations of N-demethyl menogaril in mouse plasma (9). In humans, although small peaks corresponding to N-demethylated metabolites of 7-OMEN were observed, their concentrations were negligible when compared to those of
Fig. 8. Relationship of area under the 7-OMEN plasma concentration versus time curve for individual patients to the percentage decrease in WBC observed in that same course. The curves and equations displayed were modeled as described in "Materials and Methods." 

Fig. 9. Relationship of observed percentage decrease of WBC to that predicted by the two models described in "Results" and displayed in Fig. 8. Points, individual courses of therapy.

The parent compound, mimicking the situation in mice. The 13.22-h terminal plasma half-life of 7-OMEN in humans is similar to the 10.16-h terminal half-life observed in mice (9, 10), but is much longer than the 2.66-h terminal half-life observed in rabbits (9). On the other hand, the total body clearance of 28.18 liter/hr/m² observed in our patients corresponded more closely to that of 43.2 liter/hr/m² observed in rabbits (9), than to that of 5.5 liter/hr/m² observed in mice (9, 10). We recognize that our sampling schedule on day 1 was limited to 24 h after drug administration by the treatment administered on day 2. Although a more ideal sampling schedule would have included times at three to four half-lives after drug injection, such a schedule was unworkable in our patient population with the treatment schedule used. Still, sampling at 24 h after drug injection approximates two half-lives which should allow reasonable assessment of the plasma pharmacokinetic parameters presented.

In humans, as in rabbits (8), neither urinary or biliary excretion of 7-OMEN and its fluorescent metabolites represented a major route of drug clearance. This again is in contrast to the behavior of doxorubicin and daunorubicin, in which biliary excretion plays a major role in drug elimination (23, 24). The fluorescent drug species present in urine and bile of humans treated with 7-OMEN were limited to parent compound and N-demethyl menogaril. We observed no didemethylated forms, conjugates, or aglycones in either urine or bile. This is in contrast to rabbits in which three and five 7-OMEN metabolites besides N-demethyl menogaril were observed in urine and bile, respectively (8). The metabolites of 7-OMEN observed in rabbit bile included the 7-deoxyaglycones of both parent compound and N-demethyl menogaril. We are unsure why such deoxyaglycones were not observed in any of the multiple bile samples collected from our patients. The fact that only approximately 10% of an administered dose of 7-OMEN can be accounted for in bile and urine raises the issue of which processes play major roles in drug clearance. In animal studies, little of the administered dose of drug could be accounted for as fluorescent drug forms when tissues were extracted and analyzed (8). Metabolism to nonfluorescent metabolites may therefore represent the major route of drug clearance. The existence of this metabolic pathway for other anthracyclines has already been documented by our laboratory (27). Unfortunately, suitable radiolabeled 7-OMEN, which would greatly facilitate further investigation of this question, is not available at present.

We believe that the data presented provide more than additional information about anthracycline pharmacology. The ability
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Fig. 10. Relationship of area under the 7-OMEN plasma concentration versus time curve for individual patients to the percentage decrease in absolute neutrophil (PMN) count observed in that same course. The curves and equations displayed were modeled as described in "Materials and Methods."

\[
\% \text{ΔPMN} = 100 \left( 1 - e^{-0.095 \text{AUC}} \right)
\]

OBSERVED = 1.02; EXPECTED = 3.11

Fig. 11. Relationship of observed percentage decrease in absolute neutrophil (PMN) count to that predicted by the two models described in "Results" and displayed in Fig. 10. Points, individual courses of therapy.

\[
\% \text{ΔPMN} = \frac{(100 \text{AUC}^{1.72})}{(723)^{1.72} + \text{AUC}^{1.72}}
\]

OBSERVED = 0.984; EXPECTED = 0.47

PREDICTED CHANGE IN PMN (%)

AUC (\(\mu\)M/hr)

100-95 90 85 80 75 70 65 60 55 50 45 40 35 30 25 20 15 10 5 0

\% \text{ΔPMN} = 100 \left( 1 - e^{-0.095 \text{AUC}} \right)

To correlate pharmacokinetics and pharmacodynamics, while an established concept for many other types of drugs, is still a relatively uncommon occurrence for antineoplastic agents. To some extent this reflects the relatively long temporal lag between establishment of a pharmacokinetic "milieu" by drug administration and the pharmacodynamic manifestations resulting from that administration. Our approach to the modeling of our data was empiric and used models known to produce curves the shape of which seemed appropriate for our data. As such, our choices of models do not necessarily reflect concepts of the mechanistic relationship of 7-OMEN pharmacokinetics to pharmacodynamics. Rather, they provide a mathematical description which might prove useful in dosing of patients. At present, our mathematical models do not fulfill this promise since a critical piece is still missing, i.e., the ability to predict the pharmacokinetic behavior of 7-OMEN in an individual patient. Our pharmacokinetic data lead us to believe that assessment of renal function will not be as important as assessment of hepatic drug-metabolizing capability. However, we are currently attempting to correlate both renal function, as assessed by serum creatinine and creatinine clearance, and hepatic function, as assessed by liver function tests and indocyanine green and antipyrine clearances, with the liver pharmacokinetics and pharmacodynamics of 7-OMEN.

ACKNOWLEDGMENTS

We thank H. Chlewicki and B. Knickman for excellent secretarial assistance.

REFERENCES


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