Phase I Study and Pharmacokinetics of Menogaril (NSC 269148) in Patients with Hepatic Dysfunction

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ABSTRACT

We performed a phase I study of menogaril to determine if dosage reduction was required in patients with hepatic dysfunction and if the relationship between pharmacokinetics and leukopenia, previously defined in patients with normal hepatic and renal function, was altered. Eighteen patients received 27 courses of menogaril, of which 26 were evaluable for toxicity. Patient characteristics were median age, 63 years (range, 28–80 years), 14 male/4 female, and median Karnofsky performance status 80% (range, 60–100%). Prior therapy included none, five; chemotherapy only, seven; radiotherapy only, two; and chemotherapy and radiotherapy, four. Menogaril was administered as a 2-h i.v. infusion every 28 days at 62.5 (one patient), 125 (eight patients), 187.5 (seven patients), and 250 mg/m2 (six patients), based on pretreatment serum bilirubin, aspartate aminotransferase, alanine aminotransferase, and alkaline phosphatase. Patients also had indocyanine green and antipyrene clearances measured before menogaril treatment. Menogaril and metabolites were assayed by high performance liquid chromatography. Dose-limiting toxicity was leukopenia. WBC nadirs occurred between days 8 and 20 (median, 15). Three patients developed platelet nadirs below 100,000/µl. Other toxicities included grade I nausea and vomiting in three patients and phlebitis at the site of drug infusion in six patients. Correlations were defined between pretreatment indocyanine green clearance and serum concentrations of alkaline phosphatase and total bilirubin. There were no correlations between pretreatment serum concentrations of bilirubin, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, indocyanine green clearance or antipyrene clearances measured before menogaril treatment. Menogaril and metabolites were assayed by high performance liquid chromatography. Dose-limiting toxicity was leukopenia. WBC nadirs occurred between days 8 and 20 (median, 15). Three patients developed platelet nadirs below 100,000/µl. Other toxicities included grade I nausea and vomiting in three patients and phlebitis at the site of drug infusion in six patients. Correlations were defined between pretreatment indocyanine green clearance and serum concentrations of alkaline phosphatase and total bilirubin. There were no correlations between pretreatment serum concentrations of bilirubin, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, indocyanine green clearance or antipyrene and menogaril clearances. Menogaril pharmacokinetics in patients with elevated serum concentrations of bilirubin, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, indocyanine green clearance or antipyrene and menogaril clearances were indistinguishable from that described in patients with normal liver function tests. There were excellent correlations between plasma area under the curve of menogaril and the percentage decrease in neutrophils. These were well described by two models previously used to study the same relationships in patients with normal hepatic and renal function. When compared to previous studies, patients with hepatic and renal dysfunction had a greater percentage decrease in WBC for any given area under the curve that did patients with normal hepatic and renal function. On the other hand, there was no difference in the relationship between percentage decrease in neutrophils and menogaril area under the curve in these two groups of patients. It is likely that menogaril dosage reduction will not be required in patients with elevated serum concentrations of bilirubin, alanine aminotransferase, aspartate aminotransferase, or alkaline phosphatase. However, confirmation of this hypothesis awaits completion of a subsequent clinical trial.

INTRODUCTION

Anthracyclic antibiotics, of which doxorubicin and daunorubicin are the most important representatives, are a major class of antitumor agents (1). However, these two agents produce considerable acute toxicity and have limited efficacy against many neoplasms. In addition, the clinical utility of these agents in responsive tumors is limited further because prolonged use produces cardiotoxicity (2) and because it has been assumed that doses must be reduced for patients with impaired hepatic function (3–5).

Menogaril (NSC 269148), a semisynthetic analogue of the anthracyclic antibiotic nogalamin, was introduced into phase I clinical trials (6–12) based on its broad spectrum of in vivo activity against animal tumors (13–15), its demonstrated activity after p.o. as well as i.v. administration (15–16), its reduced cardiotoxic potential (17–19), and the possibility of its having a mechanism of action different from that of doxorubicin (20–23). However, as with doxorubicin and daunorubicin, menogaril produces leukopenia in a dose-dependent and dose-limiting fashion (6–10).

Previous studies have also described the plasma pharmacokinetics of menogaril in beagle dogs (24), rabbits (25), mice (26, 27) and humans (10, 28–30), and our laboratory has defined the tissue distribution of menogaril in rabbits and mice (25, 26). During the performance of a phase I study at our center (6), we had the opportunity not only to define the human plasma pharmacokinetics of menogaril at multiple dosages, but also to define an excellent relationship between the plasma pharmacokinetics of menogaril in any patient and the myelosuppression resulting from menogaril therapy of that patient (28). We were also able to show that urinary excretion of menogaril and fluorescent metabolites accounted for only 5–6% of the daily dose, with parent compound representing ≥80% of urinary drug fluorescence after 24 h. Furthermore, in two patients with biliary tract drains, biliary excretion of drug fluorescence accounted for 2.2–4.2% of the daily dose with menogaril as the major fluorescent biliary species.

The fact that only a small percentage of an administered dose of menogaril was excreted by the kidneys and through biliary excretion combined with the previously observed relationship between menogaril AUC and degree of myelosuppression raised the question of whether reduction of menogaril dosage would be required in patients with hepatic dysfunction and led to the phase I study described in this manuscript.

MATERIALS AND METHODS

Patient Selection and Evaluation. All patients entering this trial had to fulfill the following criteria: histological proof of a malignant disease which had failed conventional chemotherapy or for which no conventional chemotherapy existed; recovery from all toxicities of prior treatments and passage of at least 4 weeks since any prior chemotherapy or radiation therapy; a minimal life expectancy of 12 weeks; a Karnofsky performance status of at least 60%; adequate bone marrow function (WBC at least 3,500 cells/µl and platelet count at least 100,000/µl); and an ejection fraction of at least 45%; assessed by resting multigated analysis scan. All patients had abnormal liver function studies and/or elevated serum urea nitrogen or creatinine. Objective measurable disease was desirable but not required. Patients who had received more than 450 mg/m2 of doxorubicin or who had congestive heart failure were excluded from study. Before entry into this study, each patient

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2 To whom requests for reprints should be addressed.

3 The abbreviations used are: AUC, area under the curve of plasma drug concentration versus time; ICG, indocyanine green; HPLC, high performance liquid chromatography; CLm, total body clearance.
had the investigational nature of the treatment explained and signed an informed consent which had been approved by the institutional review board and the National Cancer Institute.

Before entry into the study, each patient had a detailed history taken and physical examination performed. Tumor measurements were made and performance status was assessed. Pretreatment laboratory studies included hemocrit, WBC count with differential, platelet count, serum electrolytes, urea nitrogen, creatinine, total bilirubin, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, and lactate dehydrogenase. In addition, each patient had a pretreatment chest roentgenograph and electrocardiogram. Finally, patients were requested to undergo pretreatment assessment of their ICG and antipyrine clearances. Patients with histories of allergies and adverse reactions to iodides or ICG were excluded from receiving this agent. Patients with glucose 6-phosphate dehydrogenase deficiency or a history of adverse reaction to antipyrine were excluded from receiving that agent. All patients receiving ICG or antipyrine were informed of the investigational nature of the study and signed an informed consent that had been approved by the institutional review board. ICG was administered as a single i.v. bolus at a dosage of 0.5 mg/kg. Samples of heparinized blood (5 ml) were drawn prior to and at 3, 6, 9, 12, 15, 18, and 21 min after ICG injection. Plasma was prepared by centrifuging the blood at 1000 x g for 10 min and the concentration of ICG was determined spectrophotometrically at 800 nm (31). ICG clearance was calculated from the decay of plasma ICG concentration with time (31).

Antipyrine was administered p.o. as an aqueous solution at a dosage of 15 mg/kg. Samples of heparinized blood (5 ml) were obtained at 3, 6, 12, 18, and 24 h after antipyrine ingestion and were centrifuged at 1000 x g for 10 min. The resulting plasma supernatant was frozen at −20°C until analysis. Antipyrine concentrations were determined by HPLC as follows: 1 ml of plasma was mixed with 10 μl of a 200-μg/ml solution of phenacetin internal standard and was then extracted with 2 ml of chloroform. Chloroform extracts were evaporated to dryness under nitrogen and then reconstituted in 100 μl of mobile phase. Eighty μl of the reconstituted samples were injected onto the HPLC system. The HPLC system consisted of a mobile phase of methanol:0.1 M phosphate buffer, pH 7 (45:55, v/v) that was pumped at 1.6 ml/min by a Waters Model 510 pump (Waters Associates, Milford, MA) through an Alltech (Alltech Associates, Deerfield, IL) 10-μm C18 reverse phase column (25 cm x 4.6 mm) and a guard column (7 cm x 2.1 mm) packed with 30–38 μm COPPEL ODS (Whatman, Inc., Clifton, NJ). Antipyrine and phenacetin were detected at 254 nm with a Perkin Elmer LC85 spectrophotometric detector (Perkin-Elmer, Norwalk, CT) and the areas under peaks were integrated with a Waters Model 740 integrator. Concentrations of antipyrine were calculated by comparison of the area of the antipyrine peak with that of the internal standard. Under these conditions antipyrine eluted at approximately 4.97 min and internal standard eluted at approximately 8.24 min. The limit of detection for antipyrine was 0.2 μg/ml and the coefficient of variation was consistently <5%. Antipyrine clearance was determined as for ICG.

Menogaril Dosage Preparation and Administration. Menogaril (NSC 269148), was supplied in freeze-dried dosage form by the Investigational Drug Branch, National Cancer Institute, Bethesda, MD. Menogaril was reconstituted by adding 10 ml of sterile water for injection (USP) to each vial. The resulting solution contained 50 mg of menogaril, 100 mg of mannitol, and 16.6 mg of L-lactic acid. This was further diluted to a total volume of 250 ml with sterile 5% dextrose in water and infused over 2 h. Courses were repeated every 28 days, provided that the patient had recovered from any drug toxicity and had at least stable disease. Antiemetics were given with each course.

Dose Determination for Each Patient. Menogaril dosage was empirically based on the most abnormal pretreatment hepatic function test. Patients with serum concentrations of bilirubin, aspartate aminotransferase, alanine aminotransferase, or alkaline phosphatase less than twice the upper limits of normal received menogaril at 250 mg/m². Patients with values of any of the above serum chemistries that were 2–4 times the upper limit of normal received a 25% reduction in menogaril dosage. Patients with any value 4–6 times the upper limit of normal received a 50% reduction in menogaril dosage, and those with any value 6–10 times the upper limit of normal received a 75% reduction in menogaril dosage. Patients with any value greater than 10 times the upper limit of normal were ineligible to receive menogaril. No dosage reduction was instituted for any elevated serum creatinine or reduced creatinine clearance, regardless of the severity of the abnormality.

Sample Acquisition. Heparinized blood samples were obtained before and at multiple times during and after the menogaril infusion. Blood was obtained prior to and at 0.5-h intervals during the menogaril infusion. Blood samples were also obtained at the end of infusion, and at 10, 20, 30, 60, 120, 240, and 360 min, and 18 and 24 h after the cessation of the infusion. Blood samples were immediately centrifuged and plasma was removed. Plasma and plasma supernatants were immediately removed and frozen at −20°C until analyzed.

Extraction and Chromatographic Analysis of Menogaril and Metabolites. Menogaril and metabolites were analyzed by the HPLC method of McGoven et al. (32) as validated in our laboratory (25, 26, 28).

Pharmacokinetic and Pharmacodynamic Analyses. Computer modeling of the decline in plasma concentrations of menogaril was performed with MLAB (33), a computer program which performs iterative, weighted, nonlinear, least-squares regression. Based on visual inspection, estimates of initial concentrations and rate constants of elimination were made by graphic analysis, and curves were fit, assuming a nonlinear model of elimination by the reciprocal of the variance of assayed duplicates. CLmenogaril was calculated as dose divided by the area under the curve of plasma menogaril concentrations versus time (from zero to infinity).

The relationships between percentage changes in WBC or neutrophils versus AUC were modeled with ADAPT (34), a computer program which uses a Nelder-Mead search algorithm in its performance of iterative, weighted, nonlinear, least-squares regression. Two models were used: (a) percentage change = 100 (1 - e−K×AUC), where k is a fitted parameter and reflects the sensitivity of the effect to the change in AUC. It dictates the rate at which the curve approaches 100% and (b) a modification of the Hill equation (35)

\[
\text{Percentage change} = \frac{(\text{Maximum effect}) (\text{AUC}^*)}{(\text{AUC}^0) + (\text{AUC}^*)}
\]

In this model the maximum effect is a 100% reduction in WBC or neutrophils, AUC0 is the AUC associated with production of 50% of the maximum effect, and k represents Hill's constant, a parameter which allows the curve to assume a wide range of shapes.

Statistical Analyses. The significance of relationships between observed versus fitted or predicted changes in platelet counts was examined with linear least-squares regression and correlation analysis. Correlations between menogaril CLmenogaril versus the values of liver function tests (including ICG and antipyrine clearances) were similarly evaluated. The comparison of menogaril CLmenogaril determined in this population of patients with impaired hepatic or renal function versus the menogaril CLmenogaril measured by us previously in patients with normal organ function was accomplished with a two-tailed t test comparison of two independent means. Comparison of the population estimates of the fitted pharmacodynamic parameters (k, AUC0) for the current patients versus those in patients with normal hepatic and renal function was similarly accomplished based on the difference in the parameter values and their SE of the estimate.

RESULTS

Patient Population. Eighteen patients received 27 courses of menogaril, 26 of which were evaluable for toxicity (Table 1). One patient died of rapidly progressive disease 15 days after his first course of menogaril. There were 14 males and 4 females with a median age of 63 years (range, 28–80 years) and a median performance status of 80% (range, 60–100%). Five patients were previously untreated, seven had received prior chemotherapy, two had received prior radiation therapy, and
four had received both prior chemotherapy and radiation therapy. Although there were a number of tumor types represented among the patients treated, there was a preponderance of colorectal carcinoma (Table 1). This relatively large number of patients with colorectal cancer reflects both the pattern of previously treated patients referred to our institution at the time of the study and the proclivity of colorectal carcinoma to produce hepatic metastasis and related elevations of hepatic function tests.

Hematological toxicity. Dose-related leukopenia and thrombocytopenia were observed as previously described (6-11) and varied from grades 1-4 in severity (Table 2). As in patients with normal hepatic and renal function, menogaril produced more leukopenia than thrombocytopenia (Table 2). Moreover, the relationships between menogaril dosage and the resulting leukopenia and thrombocytopenia were almost identical to those defined in our previous phase I trial in which dosages of menogaril may be required to assess this question definitively.

Responses. There were no major objective responses observed among the 18 patients with measurable disease who received at least one course of menogaril therapy.

Hepatic Function Tests. A wide variety of alterations in hepatic function tests was encountered among the patients entered into this study (Table 3). Although ICG and antipyrine clearances were also performed in the majority of patients, these added studies did not prove helpful in defining more precisely the hepatic function of the population. As expected, there were significant correlations between serum concentrations of all'anine phosphatase or bilirubin and ICG half-life, with the former relationship being better than the latter (data not shown). In contrast, there were no correlations observed between antipyrine clearance and the serum concentrations of bilirubin or any hepatic enzyme.

Pharmacokinetics. At all times, menogaril was the major fluorescent drug species present 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.

There were no systematic differences among the pharmacokinetic parameters of menogaril determined at the four dosages used in this study (Table 4). At all dosages, plasma concentrations of menogaril rose progressively during the drug infusion, after which they decayed in biexponential fashion with $t_{1/2a}$ 0.16 ± 0.04 (SE) and $t_{1/2b}$ 15.30 ± 1.69 h (Table 4). These values and those determined for the steady state volume of distribution were remarkably similar to those previously reported by us in patients with normal hepatic and renal function (28) (Table 4). These pharmacokinetic parameter values do, however, differ somewhat from those reported by Dodion et al. (36) [$t_{1/2b}$ 29.6 ± 23.9 h, $CL_{TB}$ 20.2 ± 9.2 (SD) liter/h/m²; $n$ = 12]. These differences could be due to either true differences between patient samples or the fact that Dodion et al. (36) more appropriately sampled for 96 h after the dose and thereby more precisely characterized the terminal portion of the serum concentration versus time curve.

The pharmacokinetics of menogaril was linear over the four doses studied, the AUC increasing linearly with increasing dosage (Fig. 1). This relationship between menogaril dosage...
MENOGARIL IN PATIENTS WITH ORGAN DYSFUNCTION

Table 3 Alterations in hepatic and renal function tests measured prior to menogaril administration

<table>
<thead>
<tr>
<th>Elevation above upper limit of normal</th>
<th>Alkaline phosphatase (no. of patients)</th>
<th>Bilirubin</th>
<th>Aspartate aminotransferase</th>
<th>Alanine aminotransferase</th>
<th>Creatinine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>9</td>
<td>5</td>
<td>9</td>
<td>9</td>
<td>15</td>
</tr>
<tr>
<td>1-2 × normal</td>
<td>4</td>
<td>2</td>
<td>7</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>2-4</td>
<td>6</td>
<td>4</td>
<td>3</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>4-6</td>
<td>7</td>
<td>2</td>
<td>3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>6-10</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Table 4 Dose (mg/m²) 187.5 125 62.5

<table>
<thead>
<tr>
<th>Dose (mg/m²)</th>
<th>No. of studies</th>
<th>t₀ (h)</th>
<th>t₁/₂ (h)</th>
<th>CLₜ⁰ (liter/h/m²)</th>
<th>Steady state volume of distribution (liter/m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>250</td>
<td>6</td>
<td>0.13 ± 0.03*</td>
<td>13.22 ± 2.53</td>
<td>27.65 ± 4.92</td>
<td>376 ± 47</td>
</tr>
<tr>
<td>187.5</td>
<td>4</td>
<td>0.08 ± 0.03</td>
<td>24.37 ± 2.45</td>
<td>26.96 ± 15.13</td>
<td>512 ± 50</td>
</tr>
<tr>
<td>125</td>
<td>5</td>
<td>0.16 ± 0.06</td>
<td>11.53 ± 1.00</td>
<td>40.50 ± 5.20</td>
<td>440 ± 11</td>
</tr>
<tr>
<td>62.5</td>
<td>1</td>
<td>0.05</td>
<td>18.77</td>
<td>19.50 ± 4.16</td>
<td>461</td>
</tr>
</tbody>
</table>

Mean: 0.16(0.19)* 15.30(13.22) 31.88(28.18) 409(370)

SD: 0.15(0.20) 6.53(7.39) 16.63(16.30) 121(126)

SE: 0.04(0.04) 1.69(1.54) 4.16(3.33) 31(25.7)

* Mean ± SE.

The current phase I trial was designed to examine whether the models previously described in patients with normal hepatic and renal function applied to individuals with organ dysfunction. This allowed exploration not only of whether hepatic dysfunction affected the disposition of menogaril but also whether patients with such abnormalities might experience the same percentage decrease in WBC or neutrophils for a given drug exposure, as measured by AUC, as did patients with normal organ function. As before, excellent relationships were defined between menogaril AUC and the percentage decrease in WBC. These relationships were defined by the first model as

Percentage decrease in WBC = 100 (1 - e⁻⁰.⁰²⁰(AUC))  (r = 0.771)

and

Percentage decrease in neutrophils = 100 (1 - e⁻⁰.⁰⁹⁰(AUC))  (r = 0.828)

See Figs. 2 and 3. The second model, a modification of the Hill equation (35), described the relationship between AUC and myelosuppression as

Percentage decrease in WBC = \frac{(100)(AUC)^{1.57}}{6.60^{1.57} + (AUC)^{1.57}}

and

Percentage decrease in neutrophils = \frac{(100)(AUC)^{1.97}}{6.63^{1.97} + (AUC)^{1.97}}

with correlation coefficients of 0.777 and 0.829, respectively (Figs. 2 and 3). There was no statistical difference between the two models with regard to their suitability in describing the data (37).

In addition to defining these relationships of WBC and neutrophil response to menogaril exposure in the current population, we were also able to compare these responses with those observed in our previous phase I trial (Figs. 2 and 3). For graphic comparison, the percentage decreases in WBC and neutrophils, predicted from the equations developed in patients with normal hepatic and renal function, were calculated for the menogaril AUC measured in each patient in the current trial.

![Fig. 1. Relationship between menogaril dosage and AUC in patients with normal (O) and abnormal (•) hepatic function. Values from normal patients are the mean ± SE (bars) as determined in a previously published study (28).](image-url)

![Fig. 2. Relationship of area under the menogaril 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." •, patients from the current study; O, patients with normal hepatic and renal function from our previous study (28).](image-url)
This predicted value was graphed versus the percentage decrease in WBC or neutrophils actually observed (Fig. 4). Examination of this data implied that the current population had a greater than predicted decrease in WBC in response to menogaril (i.e., they were more sensitive to a given exposure) but that the previously described relationship between menogaril AUC and percentage decrease in neutrophils was appropriate for the patients in the current study. Statistical analysis of this data revealed this to be the case, with the AUC₅₀ for WBC in the current study (6.60) being significantly less than the AUC₅₀ for WBC published previously (9.85; P < 0.01) (28). On the other hand the AUC₅₀ for neutrophils in the current study (6.63) was not significantly different from that published previously (7.04) (28). Although there was a statistically significant difference between the AUC₅₀ for WBC, the Hill's constants defined for both WBC (1.57) and neutrophils (1.97) in the current trial were not significantly different from those defined for WBC (1.63) and neutrophils (1.72) in patients without hepatic and renal dysfunction.

**DISCUSSION**

The anthracycline antitumor antibiotics represent a major class of antineoplastic drugs, and as do many other cytotoxic agents, they possess a low therapeutic index. Although the concept of pharmacokinetic-pharmacodynamic relationships is not in general as well defined for antitumor compounds as for other classes of drugs (35, 38–40), there is a general consensus that increased caution must be exercised when administering antitumor drugs to patients with reduced abilities to metabolize or excrete such drugs (41). For a few drugs, such as methotrexate, the pharmacokinetic-pharmacodynamic relationship is well characterized (42–44), and there is sound evidence of increased drug exposure, as expressed by increased AUC, resulting in increased drug toxicity. Early pharmacokinetic and disposition studies of daunorubicin and doxorubicin, which showed the importance of biliary excretion and hepatic metabolism in the clearance of these drugs, led to the concept of doxorubicin and daunorubicin dose reduction in patients with hepatic dysfunction, most often expressed as hyperbilirubinemia (3–5). Although this practice is well established, the pharmacokinetic-pharmacodynamic relationship for doxorubicin and daunorubicin remains poorly characterized, and the question remains open as to how well the data on which the clinical concept of dosage reduction is predicated actually supports the practice (41).

The clinical development of menogaril represents another attempt to find an anthracycline antitumor antibiotic with true advantages over doxorubicin and daunorubicin. Although initially these advantages may have been conceived of in the traditional concepts of quantitative increases in therapeutic index or qualitative alteration in the spectrum of activity or toxicity, animal and phase I pharmacokinetic metabolism and disposition studies imply that menogaril might be an anthracycline which does not require dosage reduction in patients with hepatic dysfunction (25, 28). This implication is based on evidence that neither biliary nor renal excretion of menogaril or its fluorescent metabolites are major contributors to the drug's clearance (25, 28). Our current study shows that the
pharmacokinetic behavior of menogaril in patients with hepatic dysfunction is no different from that in patients with normal serum concentrations of creatinine or hepatic enzymes (28). This lack of impact of hepatic dysfunction on a drug with serum concentrations of creatinine or hepatic enzymes (28).

dysfunction is no different from that in patients with normal 1S pharmacokinetic behavior of menogaril in patients with hepatic dysfunction is no different from that in patients with normal hepatic and renal function (6). This finding is similar to those described in this paper.

The existence of previously defined models relating the pharmacokinetics and pharmacodynamics of menogaril and the ability to show that these relationships for suppression of neutrophils and AUC are not changed significantly in our current patient population argues strongly against the need for dosage reduction in patients such as those described in this manuscript. These pharmacokinetic and pharmacodynamic observations and arguments are lent further substance by simple inspection of the relationship between dosage and myelo-suppression. In the current patient population the median and ranges of WBC nadirs observed at dosages of 62.5, 125, 187.5, and 250 mg/m² are very similar to those observed in our 23 patients with cirrhosis. Cancer Res., 40: 1263-1268, 1980.


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