

Phase I Trial and Clinical Pharmacology of Elsamitrucin¹

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ABSTRACT

Elsamitrucin (BMY-28090) is an antitumor antibiotic first described in 1985 that has significant oncolytic activity against a number of murine tumors including P388, L1210, B16 and M5076, as well as against MX1 and HCT116 xenografts. Preclinical toxicology studies of elsamitrucin revealed edema of multiple organs associated with hypoproteinemia and, at lethal doses, severe multiorgan toxicity.

We conducted a phase I clinical trial (31 patients) of elsamitrucin administered as a 10-min i.v. infusion every 3 weeks. The starting dose (0.6 mg/m²) was 1/3 of the dog low toxic dose. The maximum tolerated dose was 30 mg/m². Dose-limiting toxicity was reversible hepatic dysfunction manifested by elevated transaminase levels not associated with bilirubin, alkaline phosphatase, or lactate dehydrogenase elevations. Other toxicities included nausea, vomiting, malaise, and phlebitis.

Because the hepatic toxicity was brief and reversible, a subsequent study (18 patients) was conducted with elsamitrucin administered every 2 weeks. Reversible grade 3 hepatotoxicity was again observed at 30 mg/m². Plasma and urine samples from patients receiving doses of 0.6–36 mg/m² were analyzed for drug content. The maximum plasma concentration and area under the plasma concentration *versus* time curve values increased linearly with doses up to 25 mg/m² but not at higher doses. The terminal half-lives, total body clearances, and volume of distribution were 36–60 h, 10–19 liters/h/m², and 400–1100 liters/m², respectively. Less than 5% was excreted in the urine in 24 h as parent compound. Bile was collected from one patient with an indwelling biliary catheter. Approximately 22% of the dose was excreted in 48 h, suggesting that biliary excretion of elsamitrucin may be an important route of drug elimination. Based on reversible hepatic toxicity, the phase II recommended dose of elsamitrucin is 25 mg/m² every 2 weeks.

INTRODUCTION

Elsamitrucin (Elsaminicin A, Y-28090) was initially reported in 1985 as a product of fermentation broths of actinomycete species (1). It is structurally related to chartreusin (2) (Fig. 1). The compound has significant antitumor activity against both solid and hematological murine malignancies (P388, L1210, B16, and M5706) as well as the MX1 and HCT-116 human tumor xenografts. It is also active against a number of human tumors maintained in culture (3). Antitumor activity does not appear to be schedule dependent. In addition, the compound is known to be less active against cells which display the multiple drug resistance phenotype (4). Although its exact mechanism or mechanisms of antitumor action are uncertain, elsamitrucin is known to produce single-strand DNA breaks and inhibit both topoisomerase I and II activities (5).

Preclinical toxicological studies in rodents and dogs revealed little effect on hematological parameters (3, 5). The mouse LD₁₀³ and LD₉₀ values were approximately 20 and 45 mg/m²,

respectively. Observed toxicities in rodents included edema in multiple organs, hypoproteinemia, and testicular atrophy. At lethal doses, bone marrow, gut, hepatic, and renal toxicities were also noted. Dogs were found to be more sensitive to elsamitrucin than were rodents; administration of the murine LD₁₀ dose to dogs was associated with significant mortality. While only minor abnormalities were found in dogs treated with nonlethal doses, at lethal doses (3.12 mg/m²) there was severe dysfunction of the gut, liver, kidney, and lungs. The canine low toxic dose was 1.8 mg/m². On the basis of the preclinical antitumor activity of elsamitrucin, we conducted a phase I clinical and pharmacological trial with elsamitrucin administered as a single 10- to 20-min i.v. infusion.

MATERIALS AND METHODS

Patient Eligibility. Patients with refractory solid tumor malignancies not involving the bone marrow were registered for this clinical trial. All patients were required to have normal peripheral blood cell counts (absolute granulocyte count, >1500/ml, platelet count, >100,000/ml) as well as normal renal (creatinine, ≤1.5 mg/dl) and hepatic (bilirubin, ≤1.5 mg/dl) function. They were also required to have a performance status of 0, 1, or 2 (Eastern Cooperative Oncology Group criteria) and an expected survival of at least 12 weeks. CBC, with differential and platelet counts, was evaluated during the study twice weekly and biochemical screening tests were conducted once weekly. After hepatic toxicity was noted, daily serum transaminase levels were determined for 1 week following each infusion or until normalization of abnormal values. All patients signed an informed consent in keeping with the policies of The University of Texas M. D. Anderson Cancer Center.

Clinical Study Design. The starting dose was 0.6 mg/m², equivalent to one-third of the low toxic dose in dogs. Three elsamitrucin-naive patients were treated at each dose level. Doses for subsequent groups of patients were based on the toxicity observed at each dose level using the following schema: no toxicity, 100% escalation; grade 1 toxicity, 50% escalation; grade 2 toxicity, 25% escalation. The dose was escalated until grade 3 toxicity (National Cancer Institute criteria) was observed in more than one-third of the patients. Individual patients could receive escalated doses if no toxicity was observed in any patient receiving the preceding dose level. Once any level of toxicity was observed, administration of escalated doses was prohibited. Patients were observed for at least 2 h after each infusion.

Pharmacokinetic Samples. Blood samples were collected with EDTA at the following times: prior to drug administration, at the end of infusion, and at 0.25, 0.5, 0.75, 1, 1.5, 3, 4, 6, 8, 24, 48, 72, 96, 120, and 144 h after the start of the infusion from most patients. At the highest dose levels additional samples were collected from patients on days 7, 8, 9, 10, and 12. Plasma was generated by centrifugation at 1500 × g for 10 min at 5°C and was stored at -70°C until analyzed. Urine samples were collected predose and at the following intervals after drug administration: 0–6, 6–12, and 12–24 h. Urine was stored at -20°C until analyzed for drug content.

Analytical Methods. Plasma, bile, and urine concentrations of elsamitrucin were analyzed by a validated high-performance liquid chromatography procedure (6). Plasma (1 ml) was added to 0.5 ml of 0.2 M phosphate buffer (pH 8.0) and 125 ng of 1-naphthol (internal standard) in 25 μl of MeOH and 5 ml of ethyl acetate. After the solution was mixed and centrifuged, 4 ml of the ethyl acetate layer was removed and evaporated to dryness, and the residue was dissolved in 250 μl of mobile phase and injected (200 μl). To 1 ml of urine was added 100 μl of

Received 9/5/91; accepted 1/6/92.

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¹ Published in part in abstract form (Proc. Am. Assoc. Cancer Res., 30: 175, 1991).

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³ The abbreviations used are: LD₁₀ (LD₉₀), lethal dose producing 10% (90%) mortality; C_{max}, maximum plasma concentration of drug; AST, aspartate aminotransferase; ALT, alanine aminotransferase; AUC, area under the plasma concentration *versus* time curve.

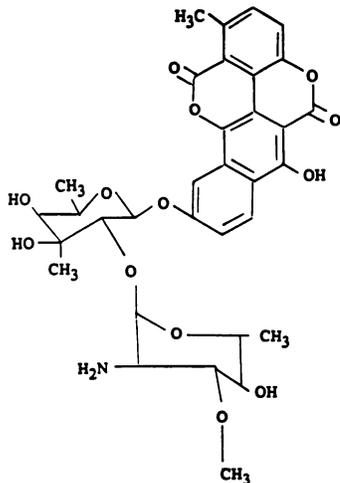


Fig. 1. Structure of elsamitrucin.

MeOH and 1.0 ml of 0.5 M succinate buffer (pH 4.0). After the solution was mixed (30 s) and sonicated (1 min), it was filtered in an Amicon Centrifree micropartition unit and injected. An IBM C8 column (5 μm) and fluorescence detection (excitation, 254 nm; emission filter, 418 nm) were used for both analyses. The mobile phases for plasma and urine were H₂O/CH₃CN (7:3, v/v) and H₂O/CH₃CN/MeOH (6:3:1, v/v), respectively, with 1.5 ml of 85% H₃PO₄ and 1.5 ml of triethylamine/liter. The standard curves were linear from 1–50 ng/ml of plasma and from 10–1000 ng/ml of urine.

Pharmacokinetic Data Collection and Calculations. Analytical data were collected, stored, integrated, calculated, and reduced to an output file on a Hewlett-Packard model 3357 laboratory automation system. The output file, containing response values and identification parameters, was electronically transferred to an IBM mainframe computer where the data were coalesced, calculated, and plotted. Statistical and pharmacokinetic values were calculated, tabulated, and plotted with SAS software (SAS Institute, Inc.) on an IBM mainframe computer (7, 8).

The regression of the weighted (1/concentration) peak height ratio of elsamitrucin to internal standard in plasma and of the peak height in urine *versus* concentration of elsamitrucin in the standards was calculated by least-squares linear regression analyses. The concentration in the samples was estimated by inverse prediction (9). Outliers were evaluated by the method of Prescott (10). If the predicted concentration of a sample was less than the lowest standard, the predicted concentration was reported as less than the lower limit of quantification. If the predicted concentration was greater than 100% of the highest standard, the samples were diluted and reanalyzed.

Plasma concentration (*C*) *versus* time (*t*) data were analyzed using noncompartmental methods and moment analysis. Observed peak plasma concentrations and the time of occurrence were tabulated. The best-fit terminal log-linear portion of the data was determined by least-squares linear regression analysis (9) of the data. The data were fit to the function:

$$\ln C = \ln B - bt$$

starting with the last 3 data points for which *C* was >0. The last point at which *C* > 0 was defined as point *n*. With this procedure, data points were added one at a time until 24 h (point *m*) was reached. The terminal log-linear portion was then defined as that portion yielding the smallest mean-square error. The slope (*b*) of this portion was used to define the half-life (*t_{1/2}*) by the following equation:

$$t_{1/2} = \ln \frac{2}{b}$$

The areas under the *C versus t* (*AUC_{inf}*) and the *t · C versus t* (*AUMC_{inf}*) curves were calculated by the trapezoidal rule and in the log-linear

portion from point *m* to point *n*, by the log trapezoidal rule (11).

Mean residence time (MRT) in the body was calculated by the following equation (12):

$$MRT = MRT_{inf} - \frac{T}{2} = \frac{AUMC_{inf}}{AUC_{inf}} - \frac{T}{2}$$

where *T* is the infusion time in h.

Total body clearance (*Cl_{tb}*) was calculated by dividing the dose of elsamitrucin in μg by the *AUC_{inf}*. The apparent volume of distribution at steady state (*Vd_{ss}*) was calculated by the following relationship (12):

$$Vd_{ss} = \frac{\text{Infused dose} \cdot AUMC_{in}}{(AUC_{inf})^2} - \frac{\text{Infused dose} \cdot T}{2 AUC_{inf}}$$

where *T* is the infusion time.

RESULTS

The clinical trial was carried out in two parts. In the first part, 31 patients were treated with 0.6- to 30-mg/m² doses of elsamitrucin administered every 3 weeks. Because of the reversible nature of dose-limiting hepatic toxicity seen during this initial study, a second study was undertaken in which 18 patients were treated at doses of 20, 25, and 30 mg/m² every 2 weeks. Overall, 89 courses of elsamitrucin were administered. The median number of courses per patient was 2 (range, 1–4). The clinical characteristics of these patients are described in Table 1.

One patient, a 61-year-old woman with a carcinoma of the gall bladder, received 3 courses of elsamitrucin. Prior to the institution of therapy, she underwent placement of a percutaneous biliary drainage catheter. This catheter permitted biliary sampling for pharmacokinetic analyses.

Hematological Toxicity. Only one patient (4.8 mg/m²) had a decrease in hematological parameters. His WBC count decreased to 2100/dl of blood but rapidly recovered.

Nonhematological Toxicity. Nausea and vomiting (grades 1 and 2), diarrhea, and malaise occurred sporadically throughout the trial. Elsamitrucin is a vesicant, and six patients had local

Table 1 Patient characteristics

	Total	Schedule	
		Every 3 wk	Every 2 wk
No. of patients studied	49	32	17
Median age (yr) (20–77)	56	55 (20–71)	58 (36–77)
Males	27	19	8
Females	22	13	9
Performance status			
0	10	4	6
1	29	19	10
2	10	9	1
Tumor types			
Sarcoma	7	7	0
Lung	9	7	2
Colorectal	12	5	7
Bladder/genitourinary	1	1	0
Head/Neck	6	3	3
Esophagus	3	2	1
Breast	5	3	2
Melanoma	3	3	0
Gallbladder	1	0	1
Pancreas	2	1	1
Prior therapy			
Chemotherapy	48	31	18
Radiation Therapy	30	10	11
Immunotherapy	11	8	4
Median no. of regimens	2	~2 ^a	~2 ^b

^a 57 + 32 = 1.78.

^b 32 + 17 = 1.88.

Table 2 Hepatic toxicity of elsamitrucin (ALT and/or AST elevations)
 ALT: grade 1, 57-140; grade 2, 141-280; grade 3, 286-1120; grade 4, >1120.
 AST: grade 1, 36-87; grade 2, 88-175; grade 3, 176-700; grade 4, >700.

Every 3 wk schedule			Every 2 wk schedule		
Dose (mg/m ²)	Patients*	Grade	Dose (mg/m ²)	Patients*	Grade
24	1/3	2	20	4/6	1
30	1/5	1	25	5/7	1
	2/5	2		1/7	2
36	3/7	2	30	1/5	1
	1/7	4		2/5	2
				2/5	3

* Number of patients with toxicity/number of patients treated at dose level.

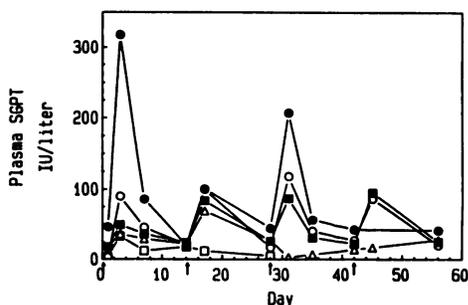


Fig. 2. Time-dependent alteration of plasma ALT (SGPT) levels in 5 patients treated with 30 mg/m² every 2 weeks. Arrows, days on which elsamitrucin was administered. Each symbol represents one patient.

irritation at the site of infusion. Although painful, no cases resulted in permanent tissue necrosis or required treatment other than ice packs and extremity elevation.

The dose-limiting toxicity was hepatic dysfunction manifested by transient ALT and AST elevations that were not associated with changes in lactate dehydrogenase or bilirubin levels. Transaminase elevations were first noted at 20 mg/m² (2 of 5 patients, grade 1) during the 3-week schedule (Table 2). At 24 and 30 mg/m², grade 2 toxicity was noted, and at 36 mg/m², 2 of 7 patients experienced grade 2 toxicity, while 1 of 7 patients experienced grade 4 toxicity.

Once hepatic toxicity was noted, transaminase elevations were followed with daily determination of ALT and AST levels. The increase in transaminase activity was rapid (maximum, day 3) and transient (always recovering by day 14). Given this rapid recovery, a second group of patients received elsamitrucin on a biweekly schedule. These patients were closely observed for hepatic toxicity. Eighteen patients were treated with doses of 20, 25, and 30 mg/m². Transaminase elevation was again the major toxicity noted (Table 2). At 30 mg/m², 2 of 5 patients had reversible grade 3 toxicity. At doses >24 mg/m², 5 patients received 3 (one patient) or 4 (4 patients) courses of elsamitrucin. There was no evidence of cumulative hepatic dysfunction. Two patients with significant enzyme elevation had similar abnormalities after each infusion. This was similar to patients receiving 2 courses. An example of this pattern is shown in Fig. 2. One patient complained of a rash.

One patient, a 52-year-old man with metastatic malignant melanoma, died during the study. Prior to treatment, he had received numerous chemotherapeutic and biological agents. He tolerated the infusion (36 mg/m²) well and had no evidence of hepatic toxicity. Five days after treatment, however, he complained of diffuse abdominal pain and vomiting. He was admitted to the hospital and rehydrated. Later that day, he became hypotensive with decreased pulses in the extremities and tachypneic. His condition rapidly deteriorated and he died 2 days

after admission while receiving antibiotics, vasopressors, and heparin. An autopsy was not performed. Although the patient had evidence of pneumonia and a myocardial infarction, the cause of death is uncertain and may have been related to elsamitrucin.

While one patient with breast cancer had a transient decrease in the size of her chest wall metastasis, no complete or partial remissions were seen during this trial.

Pharmacokinetics. Plasma concentrations of elsamitrucin greater than the lower limit of quantitation of the analytical method (10 ng/ml) were found in patients given the initial low doses of drug; however, the limited data obtained were considered insufficient to define the true elimination half-life of the drug. The terminal elimination half-life was 47 ± 8 h (mean ± SD) with a range of 36-60 h in patients treated with doses of about 11 mg/m² or greater (Fig. 3; Table 3). The mean residence time ranged from 35-61 h, and the total body clearance was 10-23 liters/h/m² (17-55 liters/kg). The volume of distribution was large, ranging from 350-1350 liters/m² (600-2600 liters), indicating that elsamitrucin was extensively bound to tissues or pooled in a peripheral compartment.

The plasma concentrations at the end of the 10-min infusions increased linearly with doses up to at least 24 mg/m². At 30 mg/m², the peak plasma concentrations were variable and fell both below and above predictions based on the lower doses (Fig. 4A). The areas under the plasma concentration versus time curves, calculated from 0-24 h, also increased linearly with doses up to at least 24 mg/m² but were variable at doses of about 30 mg/m² (Fig. 4B). These data indicate that elsamitrucin pharmacokinetics are dose dependent up to doses of at least 24 mg/m². The clearance values for elsamitrucin in patients given doses of 11-38 mg/m² appeared to fall into two different ranges. In 7 of the 10 patients, the clearances were 10-14 liters/h/m², while in 3 patients given doses of 30 mg/m², the values were in the range of 20-23 liters/h/m². Therefore, the pharmacokinetics of elsamitrucin may be dose independent at doses >24 mg/m², but only in certain patients. These results are an excellent illustration of the lack of a relationship between the dose administered and the extent of patient exposure to a drug. Even though the same dose (30 mg/m²) was administered to 5 patients, the 8-h plasma concentrations and the areas under the plasma concentration versus time curves, and consequently the clearances, varied by as much as 2-fold between patients.

In two of the patients (patients 17 and 18; see Table 3), plasma concentrations were determined after a repeat administration of the same dose 14 and 11 days after the first dose, respectively. The clearances following the second drug administration were slightly lower in both patients than after the first dose but remained high in patient 17 and low in patient 18. The mean residence times and the half-lives were similar to

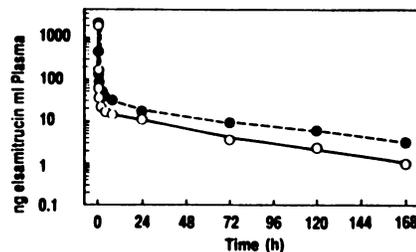


Fig. 3. Plasma concentrations of elsamitrucin as a function of time. Two patients were treated with drug (30 mg/m²) as a 10-min infusion. Patient 17 (○) exhibited high drug clearance, while patient 18 (●) had a low clearance of elsamitrucin.

Table 3 Pharmacokinetic values for elsamitrucin

Dose		Patient no.	Plasma concentration (ng/ml)		AUC (ng·h/ml)		$t_{1/2}^a$ (h)	Volume of mean residence time (h)	Clearance		Distribution ^b	
mg/m ²	mg		End of infusion	8 h	0-24 h	0-∞			liters/h	liters/h/m ²	liters	liters/m ²
10.6	20	9	1112	6.1	412	777	46.7	45.1	25.9	13.7	1178	618
16.2	26	10	1836	13.4	754	1520	36.5	41.4	17.0	10.7	704	443
24.4	48	11	2544	28.7	120	2350	36.7	40.0	20.4	10.4	816	416
29.6	58	12	1573	11.8	581	1350	55.9	61.2	43.0	21.9	2632	1340
30.5	73	14	2178	12.9	743	1321	53.4	47.6	55.0	23.1	2618	1100
30.1	52	16	4296	21.5	1964	2970	50.6	34.6	17.5	10.1	606	349
29.6	56	17	2034	14.1	892	1502	53.1	40.6	37.3	19.7	1514	800
39.9	60	18	2393	29.8	1408	2866	60.4	59.2	20.9	10.8	1237	639
29.9	43	21	2350	22.8	1252	2424	41.6	43.2	17.7	12.3	765	531
38.2	75	15	4461	28.9	1771	2971	39.9	35.5	25.2	12.8	895	454

^a $t_{1/2}$ calculated during 24-168 h interval.

^b Clearance x mean residence time.

those after the first dose. Therefore, the disposition of elsamitrucin appears to be relatively constant within an individual patient.

Analysis of the total 24-h urine output from 13 patients treated with elsamitrucin at doses of 0.6-38 mg/m² indicated that <5% of the dose was excreted by this route. With the exception of one patient, 80% or more of the parent compound excreted in 24 h was eliminated within the first 12 h. These results indicate that urinary excretion is a minor route for elimination of elsamitrucin. Therefore, the drug was cleared either by metabolism and/or by excretion in the bile or it was retained in the body for an extended period of time. However, no specific elsamitrucin metabolites were observed in this study using the present methodology.

Evidence for biliary excretion of elsamitrucin was obtained in one patient with partial external biliary drainage. About 22% of the administered dose was recovered as parent compound in the bile in 51 h with the most rapid rate of excretion occurring between 1 and 3 h after drug administration (Fig. 5). Interestingly, during this interval the bile flow rate increased from about 10 ml/min to 20-25 ml/min and then returned to 10 ml/min. Since the latter is about 25% of the normal flow rate in humans, it is possible that as much as 80% or more of the drug was excreted via the bile in this patient. If so, then biliary excretion would be the major route of excretion for elsamitrucin in humans. This would not be unexpected, based on the relatively high molecular weight (*i.e.*, 654) of the compound. However, excretion of metabolites or conjugates in the urine or bile has not been ruled out.

DISCUSSION

Elsamitrucin is a novel chemotherapeutic agent with significant preclinical *in vitro* cytotoxicity and *in vivo* antitumor activity. Its principal toxicity in humans consists of reversible hepatic dysfunction manifested by elevated serum ALT and AST levels. It does not cause myelosuppression. In this phase I study, we determined that a dose of 30 mg/m² given every 2 weeks results in transient grade 3 hepatic toxicity in about one-third of the patients treated. We conclude that 25 mg of elsamitrucin/m² administered every 2 weeks as a brief i.v. infusion is a safe dose and schedule for phase II studies.

Extensive pharmacokinetic studies were conducted in a total of 10 patients. We observed a biphasic elimination of elsamitrucin with a mean terminal half-life of 47 h. Good correlations between dose and AUC as well as C_{max} were observed at doses <30 mg/m². It is important to note, however, that at doses of

elsamitrucin of 30 mg/m² or greater C_{max} and AUC are only poorly correlated with the dose administered. At doses of about 24 mg/m² or greater, however, the 8-h plasma concentrations appeared to be predictive for those patients with higher clearance values. Plasma concentrations at 8 h were 12-14 ng/ml in the patients with high elsamitrucin clearances but 22-30 ng/ml in those with the low drug clearances values. In four patients who received elsamitrucin at 30 mg/m² and had complete

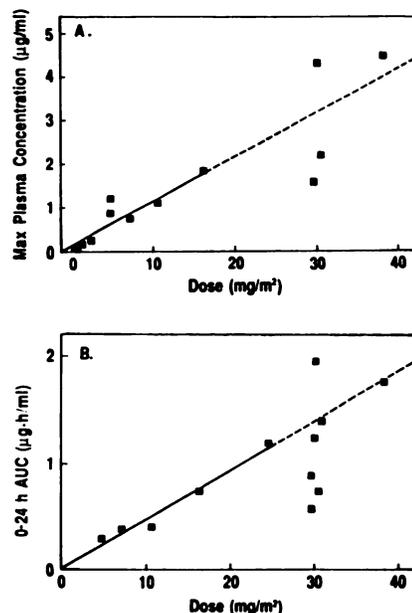


Fig. 4. Relationships between C_{max} (A) and AUC (B) with dose of elsamitrucin. Solid lines, regression lines for doses up to 24 mg/m²; dotted lines, extensions of regression lines showing where the C_{max} and AUC values would fall if the pharmacokinetics were dose linear.

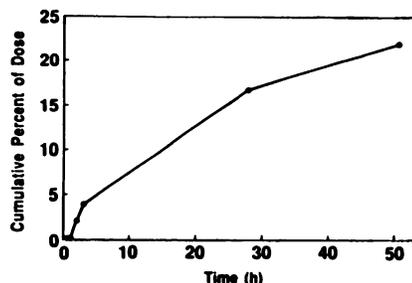


Fig. 5. Estimate of cumulative biliary excretion of elsamitrucin in a patient with a biliary fistula. The patient received a dose of 30 mg/m².

pharmacokinetic studies, there appeared to be a positive correlation between AUC and the level of transaminase elevation.

In one patient we had an opportunity to monitor biliary excretion of elsamitrucin and noted that a significant portion of the administered dose was excreted in the bile as intact drug during 48 h following drug administration. The hepatic elimination of the compound noted in our patient may be indicative of extensive biliary excretion of elsamitrucin and could possibly serve as an explanation for the transient hepatic toxicity observed in this clinical trial.

Although no real antitumor responses were noted in this phase I study, the population was made up of heavily pretreated patients with advanced cancer. It is also possible that in a less heavily pretreated group of patients the drug could be administered more frequently at a higher dose. Elsamitrucin should be pursued in single-agent phase II studies. Its unique toxicity profile suggests that, if active, it could be readily combined with other chemotherapeutic agents.

REFERENCES

1. Konishi, M., Sugawara, K., Tsurakawa, Y., Nishiyama, Y., Miyaki, T., and Kawaguchi, H. BMY-28090 a new antitumor antibiotic related to chartreusin: isolation, chemistry and activity, Abstract 320. *In: Abstracts of the 14th International Congress on Chemotherapy, Kyoto, Japan, 1985.*
2. Konishi, M., Sugawara, K., Kofu, F., Nishiyama, Y., Tomita, K., Miyaki, T., and Kawaguchi, H. Elsamicins, new antitumor antibiotics related to chartreusin. I. Production, isolation, characterization and antitumor activity. *J. Antibiot. (Tokyo)*, 29: 784-791, 1986.
3. Schurig, J. E., Bradner, W. T., Basler, G. A., and Rose, W. C. Experimental antitumor activity of BMY28090, a new antitumor antibiotic. *Invest. New Drugs*, 7: 173-178, 1989.
4. Casazza, A. M. Identification and characterization of novel topoisomerase inhibitors. *Proc. Am. Assoc. Cancer Res.*, 29: 270, 1988.
5. Schacter, L. P., and Yovan, N. Bristol Myers Squibb Investigator's Brochure: Elsamitrucin. Evansville, IN: Bristol Myers Squibb, 1990.
6. Gaver, R. C., Deeb, G., and George, A. M. Validated HPLC procedures for the analysis of BMY-28090 in human plasma and urine. *Cancer Chemother. Pharmacol.*, 25: 195-201, 1989.
7. Farnen, R. H., Muniak, J. F., and Pittman, K. A. Management of pharmacokinetic data using HP-3357/mainframe IBM interfacing. *Drug Inform. J.*, 21: 141-152, 1987.
8. Faulkner, H. C., and Farnen, R. H. Database design and management in a pharmacokinetic department. *Drug Inform. J.*, 23: 245-255, 1989.
9. Snedecor, G. W., and Cochran, W. G. *Statistical Methods*, Ed. 7, pp. 149-174. Ames, IA: Iowa State University Press, 1980.
10. Prescott, P. An approximate test for outliers in linear models. *Technometrics*, 17: 129-132, 1975.
11. Riegelman, S., and Collier, P. The application of statistical moment theory to the evaluation of *in vivo* dissolution time and absorption time. *J. Pharmacokinet. Biopharm.*, 8: 509-534, 1980.
12. Gibaldi, M., and Perrier, D. *Pharmacokinetics*, Ed. 2. New York: Marcel Dekker, Inc., 1982.

Cancer Research

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Cancer Res 1992;52:1406-1410.

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