Cancer Chemother Pharmacol (1985) 14:21–25

Cancer Chemotherapy and Pharmacology

Pharmacokinetics of amsacrine in patients receiving combined chemotherapy for treatment of acute myelogenous leukemia

J. L. Jurlina[1], A. R. Varcoe[2], and J. W. Paxton

[1] Department of Pharmacology and Clinical Pharmacology University of Auckland School of Medicine, Auckland, New Zealand
[2] Department of Haematology, Auckland Hospital, Auckland, New Zealand

Summary. *The pharmacokinetics of amsacrine have been studied after the first and third infusions (200 mg · m^{-2}) in 10 patients receiving combined chemotherapy for the treatment of acute myelogenous leukaemia (AML). Postinfusion amsacrine elimination was best described by a biexponential expression with a mean $t_{1/2\alpha}$ of 0.8 h and a terminal $t_{1/2\beta}$ of 5.3 h. After the third infusion there was a significant reduction ($P < 0.05$) in the plasma clearance (Cl) and a prolongation of the terminal half-life ($t_{1/2\beta}$) ($P < 0.01$), but no change in the initial half-life ($T_{1/2\alpha}$) or volume of distribution (Vd). No significant overall changes were recorded in any of the biochemical indices of renal or hepatic function between the first and third infusions, but the patient who exhibited the largest reduction in Cl showed a marked increase in AST levels and a reduction in albumin concentration. Two distinct groups were apparent after the first infusion, patients with a Cl > 294 and those with a Cl < 208 ml · h^{-1} · kg^{-1}. The latter patients were significantly older ($P < 0.05$), and four of the five had subnormal albumin concentrations. Urinary determination of amsacrine indicated that renal elimination plays a minor role in the total clearance of this drug. Amsacrine was also found to be highly bound to plasma proteins (96.4%–97.7%), but changes in binding were not responsible for the reduced Cl and prolonged $t_{1/2\beta}$ observed between the first and third infusions. We suggest that the elimination of amsacrine may be susceptible to small changes in hepatic function, perhaps due to the high amsacrine concentrations (5–18 μmol · l^{-1}) achieved with this regimen, which may be approaching saturation of the capacity for hepatic elimination.*

Introduction

Amsacrine (NSC 249992), 4′-(9-acridinylamino)-methanesulfon-*m*-anisidide, is one of a series of acridine derivatives synthesised as potential antitumour agents by Cain and colleagues [3–5]. Significant activity has been demonstrated against lymphomas and leukaemias [10, 12, 13, 22, 25, 26], and in combination with cytosine arabinoside (ARA-C) and 6-thioguanine (6-TG) it has proven effective for remission induction in acute myelogenous leukaemia (AML) [1, 2, 8].

Several investigations of the pharmacokinetics of amsacrine as a single agent have been reported in man [9, 15, 17, 19, 21, 23]. In these studies, plasma amsacrine concentrations were determined by monitoring radiolabelled drug [9, 24], by hydrolysis of drug to a fluorescent derivative [19, 23], or by high-performance liquid chromatography (HPLC) [15, 17, 21].

We have developed an HPLC method for the determination of amsacrine in plasma and urine [11, 18]; this method is specific for the parent drug and is free of the problems of interference from metabolites or from irreversibly protein-bound drug.

Our aim was to define the pharmacokinetics of amsacrine in patients receiving infusions of this drug in combination with ARA-C and 6-TG as treatment for AML. The effect of multiple infusions on amsacrine pharmacokinetics was also investigated.

Patients and methods

Patients. All patients were receiving amsacrine in combination with ARA-C and 6-TG for treatment of AML. Patient 2 was in relapse, whereas the remaining nine were newly diagnosed, previously untreated, patients. Details of the patients are given in Table 1. Before the first infusion, all patients had normal hepatic and renal biochemical profiles, except that patient 5 had a high aspartate amino transferase (AST) level and several patients (3, 7, 8, and 9) had low plasma albumin concentrations.

This study was approved by the local Ethical Committee, with each patient giving informed consent.

Treatment. Treatment was administered over a 6-day period. Each patient received oral doses of 6-TG (2.5 mg · kg^{-1}, twice daily, and IV doses of ARA-C (2.5 mg · kg^{-1}) on days 1–6. On days 4, 5, and 6 an IV infusion of amsacrine (200 mg · m^{-2}) was administered through a surgically implanted Hickman catheter after the morning dose of ARA-C and 6-TG. For infusion, a concentrated solution of amsacrine (50 mg · ml^{-1}) in anhydrous *N*,*N*-dimethylacetamide (Parke-Davis/Warner-Lambert, N. Z. Ltd) was diluted with lactic acid solution to give a concentration of 5 mg · ml^{-1}. The appropriate amount of drug was then added to 500 ml 5% dextrose solution, and infused over a mean of 1.5 h in the 20 infusions studied.

Blood and urine sampling. Plasma drug concentrations were followed for 24 h after the first and third amsacrine infusions in all patients. Samples (5 ml) were collected into heparinised glass tubes before, during, and at 0, 1, 2, 4, 6, 8, 10, 12, 18, 22,

Offprint requests to: J. W. Paxton, Department of Pharmacology and Clinical Pharmacology, University of Auckland School of Medicine, Private Bag, Auckland, New Zealand

Table 1. Patient characteristics and biochemical profiles during first and third infusions

Patient no.	Infusion	Age/sex	Race/wt (kg)	Albumin ($g \cdot l^{-1}$)	AAG ($g \cdot l^{-1}$)	Total protein ($g \cdot l^{-1}$)	Total bilirubin ($\mu mol \cdot l^{-1}$)	AST ($U \cdot l^{-1}$)	Serum creatinine ($\mu mol \cdot l^{-1}$)	Urea ($\mu mol \cdot l^{-1}$)
Normal				36–48	0.43–0.99	64–79	5–22	10–55	0.05–0.12	3.2–7.7
1	1	35/M	P/106.0	42	1.65	72	10	30	0.08	3.4
	3			43	1.63	70	11	20	0.10	4.3
2	1	36/F	C/56.2	37	1.87	63	10	30	0.08	4.6
	3			38	1.85	64	15	28	0.07	5.1
3	1	64/M	C/92.8	34	1.44	70	12	15	0.1	4.7
	3			36	1.24	69	15	20	0.1	3.8
4	1	32/M	P/81.5	39	1.08	64	7	20	0.09	4.4
	3			37	1.14	64	15	20	0.07	4.2
5	1	45/M	P/85.9	39	0.59	75	12	70	0.11	3.9
	3			37	0.49	71	10	25	0.08	4.2
6	1	18/M	C/81.0	40	0.95	69	11	25	0.08	5.9
	3			ND	1.03	ND	ND	ND	ND	ND
7	1	66/F	C/57.2	28	1.41	53	16	35	0.08	5.9
	3			32	1.41	ND	ND	ND	0.11	9.3
8	1	52/F	C/62.3	35	1.44	64	18	20	0.07	4.3
	3			ND	1.51	66	27	75	ND	ND
9	1	48/M	P/118.0	35	0.52	82	35	45	0.07	4.7
	3			34	0.52	ND	ND	45	0.08	4.8
10	1	36/M	C/72.5	41	1.25	77	10	30	0.08	5.1
	3			35	1.06	69	11	190	0.08	7.7

AAG, alpha$_1$-acid glycoprotein; AST, aspartate amino transferase; P, Polynesian; C, Caucasion; ND, not determined

and 24 h after the infusion. All samples were taken from the catheter via a syringe the first 5 ml blood being discarded, with the exception of the samples taken at the mid-point and at the end of infusions, which were obtained by venipuncture of an arm vein. Care was taken during blood collection to ensure that no haemolysis occurred, as this can reduce amsacrine concentrations [11]. After separation by centrifugation at 10° C, plasma was stored at −20° C until analysis, which was done within 6 weeks.

All urine passed between the time of the first and second infusions was collected, the total volume recorded, and a 20-ml specimen stored at −20° until analysis.

Amsacrine assays. Plasma amsacrine concentrations were determined in duplicate 0.5-ml aliquots by our published method [11]. This assay has good accuracy with recoveries ranging from 104%−115% over the range 0.5−10 $\mu mol \cdot l^{-1}$, and excellent precision with mean values for intra- and interassay CVs of 2.3% and 3.2%, respectively. The same procedure was used for the determination of urinary amsacrine, except that the hexane wash was omitted and an alternative internal standard, 4′-(4-methyl-9-acridinylamino)-methanesulfon-*m*-anisidide was used to avoid interferences from endogenous urinary compounds in the chromatographic separation [18].

Plasma protein binding. The plasma protein binding of amsacrine was determined by equilibrium dialysis. Duplicate 1 ml plasma samples, adjusted to pH 7.4 with CO_2, were dialysed for 4 h at 37° C against 1 ml isotonic phosphate buffer pH 7.4, containing 1 $\mu mol\ l^{-1}$ amsacrine-9-^{14}C, (a kind gift from Dr. M. A. Leaffer, SRI International, Menlo Park). The unbound fraction was determined by the ratio of $D_b'/(D_b - D_b')$, where D_b and D_b' are the dpm per ml in buffer before and after dialysis, respectively. Further details of the binding of amsacrine to plasma proteins will be published elsewhere.

Pharmacokinetic analysis. The pharmacokinetic model was selected by the AUTOAN 2 decision making programme [20], which provided initial estimates for further fitting of the post-infusion concentration-time data to an exponential expression of the form,

$$C = Re^{-\alpha t} + Se^{-\beta t} \text{———} + Ne^{-nt}$$

using NONLIN, a least squares nonlinear curve fitting programme [16]. In this expression, C represents post-infusion amsacrine concentration as a function of time; R, S and N, the extrapolated post-infusion concentration constants; and α, β and n the exponential rate constants [7].

The data were weighted with 1/C as a weighting function in the fitting procedure.

Model independent total plasma clearance (Cl) was calculated after the first infusion by the equation ($Cl = Dose/AUC_0^\infty$), where the area under the plasma concentration-time curve (AUC_0^∞) was obtained by trapezoidal rule for 0 to the last time point *(t)*, and then extrapolated to infinity by the relationship C_t/β (where C_t is the estimated concentration at the last time point calculated from the terminal linear relationship, and β is the terminal slope). Low amsacrine concentrations were detectable prior to the third infusion and

obviously contributed to the AUC calculated for the third infusion. For most patients this preinfusion concentration was less than or equal to 0.5 μmol · l^{-1}, but the two patients with the longest half-lives had values of 1.34 and 1.62 μmol · l^{-1}. The AUC for the third infusion was corrected for this drug residue from the second infusion by not including the extrapolated tail portion of the third infusion. As the 'tail portion' of the second infusion might be expected to be less than or equal to the tail portion of the third infusion, this might have led to overcorrection in the AUC value, and thus a clearance value higher than the true value after the third infusion. The apparent volume of distribution (Vd), corrected for the subjects weight (W), was calculated from the equation $Vd = Cl/\beta.W$.

Results were analysed for statistical significance using the Wilcoxon matched-pairs signed-ranks test for paired, and the Mann-Whitney U-test for unpaired data.

Results

Typical plasma concentration-time profiles from two patients are illustrated in Fig. 1. Computer analyses indicated that all the elimination curves could best be fitted by a biexponential expression. Thus, the pharmacokinetics of amsacrine in these patients are best described by a two-compartment open model. The half-lives derived from the NONLIN fit and model independent parameters (Cl and Vd) are presented in Table 2. Large interindividual variations were observed in all parameters. However, within-patient comparisons indicated that while overall there was no significant change in the $t_{1/2\alpha}$ between the first and third infusions, nine of the ten patients had a longer $t_{1/2\beta}$ after the third infusions, and the difference was highly significant ($P < 0.01$). Eight of these patients also had a significantly lower plasma Cl after the third infusion ($P < 0.05$), but no significant change in the Vd. Comparison within each patient of the available biochemical parameters measured during the first and third infusions indicated no overall significant differences. However, the patient who exhibited the greatest reduction in Cl (approximately 55%) showed marked differences in AST levels (30–190 U · l^{-1}) and a marked reduction in albumin concentration from 41 to 35 g · l^{-1} during the first and third infusions. Interestingly, the Cl values after the first infusion appeared to fall into two distinct groups, five patients with Cl > 294 and five patients with Cl < 208 ml · h^{-1} · kg^{-1}. The patients in the latter group were significantly older ($P < 0.05$), with a mean age of 53 years, as against 33 years for the former group. In addition, the older group had significantly lower albumin concentrations ($P < 0.05$), four of the five having albumin concentrations below the lower limit of normal. After the third infusion, the young patient (no. 10) referred to above moved from the high to the low clearance group.

The amount of unchanged amsacrine excreted in the urine was studied in six patients between the first and second drug infusions, a period of approximately 24 h. During this time, 2%–10% (mean 5.0% ± 3.1%, SD) of the dose was excreted unchanged. In all patients the concentration of amsacrine in

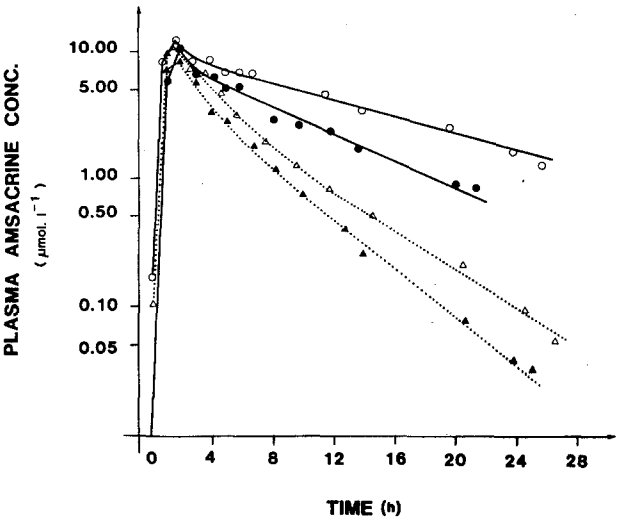

Fig. 1. Plasma amsacrine concentration-time profiles following the first *(closed symbols)* and third infusions *(open symbols)* in two AML patients (▲, △, patient 6: ●, ○, patient 7)

Table 2. Amsacrine pharmacokinetic parameters calculated after first and third infusions

Patient no.	Dose (mg)	Infusion time (h)		Conc.[a] (μmol · l^{-1})		$t_{1/2\alpha}$ (h)		$t_{1/2\beta}$ (h)		Cl (ml · h^{-1} · kg^{-1})		Vd (l · kg^{-1})		% Unbound		% Urinary excretion
		1	3	1	3	1	3	1	3	1	3	1	3	1	3	1
1	400	2.45	1.25	9.09	9.64	0.31	0.44	4.15	4.38	208	181	1.24	1.14	2.39	2.49	4.06
2	315	0.58	0.58	10.54	10.12	0.20	1.78	3.67	5.88	294	288	1.56	2.44	2.68	3.01	ND
3	420	3.67	0.75	7.84	17.43	0.36	0.23	5.55	8.73	171	126	1.37	1.59	2.78	2.70	2.13
4	410	0.75	2.25	11.13	6.65	0.43	1.50	3.29	4.46	299	304	1.42	1.96	3.40	3.27	2.01
5	400	1.58	1.62	5.86	7.80	1.66	0.37	4.38	4.58	350	290	2.21	1.92	3.02	3.23	ND
6	420	1.67	1.47	8.16	10.16	0.89	1.60	3.05	3.95	356	289	1.57	1.71	2.73	3.02	ND
7	310	1.75	1.58	10.41	12.12	0.10	0.88	5.59	9.38	201	126	1.62	1.64	3.42	2.98	10.39
8	325	1.00	1.83	14.53	14.61	0.36	0.28	5.22	4.71	158	174	1.18	1.19	2.61	2.32	6.46
9	450	2.67	1.67	6.67	5.91	0.40	0.90	6.97	7.57	197	194	1.98	2.12	3.54	3.52	ND
10	380	1.50	1.17	8.49	10.79	1.43	1.57	5.16	5.85	339	152	2.52	1.29	2.78	3.07	4.69
Mean		1.76	1.42	9.27	10.53	0.61	0.96	4.70	5.95	257	212	1.67	1.70	2.93	2.97	4.96
SD		0.94	0.50	2.5	3.5	0.53	0.61	1.22	1.95	78	73	0.44	0.42	0.40	0.34	3.14
Significance		NS		NS		NS		$P < 0.01$		$P < 0.05$		NS		NS		

[a] Concentration at end of infusion
ND, not determined; NS, not significant

the last urine sample obtained prior to commencement of the second infusion was still measurable. Thus, the absolute fraction of unchanged amsacrine excreted in the urine would be greater than this 24-h value.

Protein-binding studies of amsacrine in postinfusion plasma samples indicated that this drug is highly bound, with a mean unbound fraction of 2.95% ± 0.38% (SD), range 2.39%−3.54% in the ten patients studied. This value was not significantly different from that [2.98% ± 0.83% (SD), range 1.67%−4.1%] found in plasma from 12 healthy subjects, despite significantly higher albumin concentrations and significantly lower alpha$_1$-acid glycoprotein concentrations in the normal group. In addition, no significant difference was observed in binding between samples from the first and third infusions or between the old and young patient groups.

Discussion

This study has investigated the pharmacokinetics of amsacrine at higher doses than have hitherto been reported, and following multiple doses of drugs as part of combination chemotherapy. The biexponential elimination curves observed are in agreement with other studies [9, 19, 23].

The elimination of amsacrine from the body appears to take place mainly by way of hepatic extraction and metabolism; only a small fraction of unchanged drug was excreted by the kidneys. Our urinary results are supported by Hall et al. [9], who found 12% excreted in the urine as unchanged amsacrine over 72 h in four patients with normal renal and hepatic function. Evidence from animal studies has also suggested that the liver is the major organ for the elimination of amsacrine [6].

Several explanations for the prolonged elimination half-life and reduced clearance of amsacrine after the third infusion are possible.

Alterations in the plasma protein binding of a drug may significantly affect its kinetics [14]. However, we observed no change in the degree of amsacrine binding in plasma between the first and third infusions and between the old and young patient groups, despite subnormal albumin concentrations in the older group.

The possibility that the altered kinetics may be due to nonlinear drug elimination cannot be discounted. Whether amsacrine exhibits concentration-dependent kinetics within the concentration range achieved in our patients is not known. Within-patient comparison of concentrations at the end of the first and third infusions indicated no overall significant increase. However, the five patients (3, 5, 6, 7, and 10) who had $> 10\%$ increase in the end of infusion concentration all exhibited the greatest reductions in clearance (by 17%−55%). The clearance changes for the remaining five patients were all $\leq 13\%$.

Another possible source for the pharmacokinetic changes associated with the third infusion is subclinical hepatocellular damage occurring during this 6-day course of intensive chemotherapy. Although no overall significant changes in the indices of liver function were evident, there was a tendency to increased bilirubin levels during the third infusion. Arlin and colleagues [1] observed a 60% incidence of hepatic dysfunction following a similar chemotherapy regimen with amsacrine, ARA-C, and 6-TG. Thus the potential for these drugs to cause liver damage does exist. In addition, in patients with pre-existing hepatic dysfunction, a significant reduction in amsacrine clearance and prolongation of terminal half-life have been reported [9]. Reduced liver capacity, or perhaps increased susceptibility to liver damage, in the older group may also provide the explanation for the difference in amsacrine clearances between the old and young group. Age in itself does not dichotomize the patients into the low and high clearance groups, as one young patient moved from the higher to the lower clearance group with the third infusion. This was accompanied by the greatest increase in AST and decrease in albumin levels observed in any of our patients from the first to the third infusion, suggesting perhaps reduced hepatic function. Apart from the lower albumin concentrations in the lower clearance group, there also was a tendency for elevated bilirubin levels in these patients.

In summary, this preliminary study has demonstrated that relatively complex elimination kinetics occur with amsacrine, with large interindividual variations in pharmacokinetic parameters apparent. We speculate that the elimination of amsacrine may be very susceptible to hepatic function, perhaps due to the high amsacrine concentrations (5−18 $\mu mol \cdot l^{-1}$) achieved with this regimen, which may be approaching saturation of the capacity for hepatic elimination. Obviously further studies on the effect of concentration and hepatic function on the pharmacokinetics of amsacrine are necessary.

Acknowledgements. JWP is a Senior MRC Research Fellow. The study was supported by a grant to JWP from the Auckland Medical Research Foundation. Thanks are extended to the nursing staff of Ward 9D, Auckland Hospital for collection of samples.

References

1. Arlin ZA, Flomenberg N, Gee TS, Kempin SJ, Dellaquila C, Mertelsmann R, Straus DJ, Young CW, Clarkson BD (1981) Treatment of acute leukaemia in relapse with 4′-(9-acridinylamino) methanesulphon-*m*-anisidide (AMSA) in combination with cytosine arabinoside and thioguanine. Cancer Clin Trials 4: 317
2. Arlin ZA, Gee TS, Mertelsmann R, Kempin SJ, Reich LM, Straus DJ, Miggins C, Clarkson BD (1983) Randomized trial of 4′(9-acridinylamino) methanesulfon-*m*-anisidide (AMSA) in combination with cytosine arabinoside (ARA-C) and thioguanine (TG) vs daunorubicin with ARA-C and TG in adults with acute non-lymphoblastic leukaemia (ANLL). In: Amsacrine. Current perspectives and clinical results with a new anti-cancer agent. Communications Media for Education, New Jersey, p 977
3. Atwell GJ, Cain BF, Seelye RN (1972) Potential Antitumour agents. 12. 9-Anilinoacridines. J Med Chem 15: 611
4. Cain BF, Atwell GJ (1974) The experimental antitumour properties of three congeners of the acridylmethane-sulphonanilide (AMSA) series. Eur J Cancer 10: 539
5. Cain BF, Seelye RN, Atwell GJ (1974) Potential Antitumour agents. 14. Acridylmethanesulphonanilides. J Med Chem 17: 922
6. Cysyk RL, Shoemaker D, Adamson RH (1971) The pharmacological disposition of 4′-(9-acridinylamino) methanesulfon-*m*-anisidide in mice and rats. Drug Metab Dispos 5: 579
7. Gibaldi M, Perrier D (1975) In: Pharmacokinetics. Marcel Dekker, New York, p 69
8. Goldman A, Malpas JS (1982) Phase I and II study of AMSA in childhood tumours. Cancer Chemother Pharmacol 9: 53
9. Hall SW, Friedman J, Legha SS, Benjamin RS, Gutterman JU, Loo TL (1983) Human pharmacokinetics of a new acridine derivative, 4′-(9-acridinylamino) methanesulfon-*m*-anisidide (NSC 249992). Cancer Res 43: 3422

10. Jacquillat C (1983) Amsacrine in acute leukaemia: In: Amsacrine. Current perspectives and clinical results with a new anti-cancer agent. Communication Media for Education, New Jersey, p 41
11. Jurlina JL, Paxton JW (1983) A high-performance liquid chromatographic method for the determination of 4′-(9-acridinylamino)methanesulfon-*m*-anisidide (AMSA) in plasma. J Chromatogr 276: 367
12. Legha SS, Keating MJ, Zander AA, McCredie KB, Bodey GP, Freireich EG (1980) 4′(Acridinylamino) methanesulfon-*m*-anisidide (AMSA): A new drug effective in the treatment of adult acute leukaemia. Ann Intern Med 93: 17
13. Legha SS, Keating MJ, McCredie KB, Bodey GP (1982) Evaluation of AMSA in previously treated patients with acute leukaemia: Results of therapy in 109 adults. Blood 60: 484
14. Lima JJ, Boudoulas H, Blanford M (1981) Concentration-dependence of disopyramide binding to plasma protein and its influence on kinetics and dynamics. J Pharmacol Exp Ther 219: 741
15. Malspeis L, Khan MN, Blat HB (1979) HPLC determination of 4′-(9-acridinylamino)methanesulfon-*m*-anisidide (M-AMSA) (NSC 249992) in the plasma of a patient with hepatic dysfunction. Proc Am Assoc Cancer Res 20: C384 (abstract 383)
16. Metzler CM (1969) NONLIN. A computer program for parameter estimation in non-linear situations. Upjohn (Biostatistics Dept), Kalamazoo
17. Micetich KC, Zwelling LA, Gormley P, Young RC (1982) Phase I–II study of *m*-AMSA administered as a continuous infusion. Cancer Treat Rep 66: 1813
18. Paxton JW, Jurlina JL (1984) Determination of the anti cancer drug amsacrine in biological fluids by HPLC. In: Methodological surveys in biochemistry and analysis, vol 14. Reid E, Wilson ID (eds) Drug determination for therapeutic and forensic appraisals. Plenum Press, London (in press)
19. Rivera G, Evans WE, Dahl GV, Yee C, Pratt CB (1980) Phase I clinical and pharmacokinetic study of 4′-(9-acridinylamino)methanesulfon-*m*-anisidide in children with cancer. Cancer Res 40: 4250
20. Sedman AJ, Wagner JC (1974) AUTOAN. A decision-making pharmacokinetic computer programme. Publication Distribution Service, University of Michigan Medical Center, Ann Arbor
21. Staubus A, Neidhart J, Young D, Malspeis L (1980) Pharmacokinetics of *m*-AMSA (NSC 249992) in humans. Proc Am Assoc Cancer Res 21: 198 (abstract 793)
22. Tan CTC, Hancock C, Steinherz PG, Steinherz LJ, Sorell M, Chan KW, Mondora A, Miller DR (1982) Phase II study of 4′-(9-acridinylamino)methanesulfon-*m*-anisidide (NSC 249992) in children with acute leukaemia and lymphoma. Cancer Res 42: 1579
23. Van Echo DA, Chiuten DF, Gormley PE, Lichtenfield JL, Scotlock M, Wiernik P (1979) Phase I clinical and pharmacological study of 4′(9-acrinylamino)methanesulfon-*m*-anisidide using an intermittent by-weekly schedule. Cancer Res 39: 3881
24. Von Hoff DD, Howser D, Gormley PE, Bender RA, Glaubiger D, Levine AS, Young RC (1978) Phase I study of methanesulfon-amide, *N*-[4-(9- acidinylamino)-3-methoxy phenyl] (*m*-AMSA) using a single-dose schedule. Cancer Treat Rep 62: 1421
25. Weick JK, Jones SE, Ryan DH (1983) Phase II study of amsacrine (*m*-AMSA) in advanced lymphomas: A Southwest Oncology Group Study. Cancer Treat Rep 67: 489
26. Winton EF, Hearn EB, Vogler WR, Johnson L, Logan T, Raney M (1983) Amsacrine in refractory adult acute leukaemia: a pilot study of the Southeastern Cancer Study Group. Cancer Treat Rep 67: 977

Received December 6, 1983/Accepted April 16, 1984