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The clinical pharmacokinetics of N-5-dimethyl-9-[(2-methoxy-4-methyl-sulfonylamino)phenylamino] -4-acridinecarboxamide (CI-921) in a phase 1 trial

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Summary. The pharmacokinetics of CI-921 were studied after 65 infusions over a 20-fold dose range (13–270 mg/m^2 per day) in 16 patients during a phase 1 trial. CI-921 was given by a 15 min infusion on three consecutive days. Plasma samples were collected after the first and third infusions, and urine, at 6 h intervals throughout the 3 days. CI-921 concentrations were measured by an HPLC method. Maximum plasma concentrations ranged from 3–86 μmol/l. The plasma concentration-time disposition curves were mainly biphasic over the 24-h postinfusion period. There was no significant difference by the paired *t*-test between the C_{max}, AUC, CL, V_{ss}, MRT, $t_{½\alpha}$, or $t_{½\beta}$ calculated for the first and third infusions. The means (range) of model-independent pharmacokinetic parameters were: CL, 158 (94–290) ml/h per kg; V_{ss}, 319 (219–614) ml/kg; MRT, 2.1 (1.1–3.5) h; $t_{½\alpha}$, 0.5 (0.2–1.1) h; and $t_{½\beta}$, 2.6 (1.1–5.0) h. There was a strong linear correlation between the dose and the AUC and C_{max}, suggesting linear kinetics over this dose range. A very small amount (< 1%) of the total dose was excreted as unchanged CI-921 in the urine, mostly in the 12-h postinfusion period.

Introduction

N-5-Dimethyl-9-[(2-methoxy-4-methylsulfonylamino)-phenylamino]-4-acridinecarboxamide (CI-921) is an analogue of amsacrine, a cytotoxic agent clinically effective against leukemias [1, 4, 11] but showing little activity against solid tumors [4–6]. CI-921 was synthesized in an attempt to develop an agent with a broader clinical antitumor spectrum than that of amsacrine. It has shown significantly greater activity in both in vitro and in vivo solid-tumor test systems [2]. The pharmacokinetics of CI-921 were studied during a phase 1 trial with escalating doses.

Patients and methods

This phase 1 trial of CI-921 was approved by the local ethical committee. Sixteen patients with solid tumors refractory to chemotherapy or for whom conventional therapy did not exist gave informed consent and entered the trial. Details of the patients are given in Table 1. All had normal renal and hepatic function as assessed by standard biochemical tests. CI-921, as the isethionate salt (from Warner-Lambert, Ann Arbor, Mich.), was dissolved in distilled water (4 mg/ml free base) and diluted in 200 ml 5% dextrose water. This was infused over 15 min into a forearm vein via an indwelling catheter by a constant rate infusion pump on three consecutive days. Where appropriate, this course of therapy was repeated every 3 weeks. A total of 39 courses were given. Doses were escalated on a modified Fibonacci regimen from 39 mg/m^2 to 810 mg/m^2 (total dose over 3 days), with three patients entered at each new dose level. In the absence of toxicity, escalation was permitted within patients in subsequent courses.

Blood and urine sampling. Blood (5 ml) from an indwelling i.v. catheter in the opposite arm was collected into heparinized tubes at 0 (blank), 7, 15 (end of infusion), 20, 30, 45, and 60 min and at 1.5, 2, 3, 4, 6, 8, 12, 18, and 24 h after the first and third infusions, with additional samples taken at 36, 48, 72, and 96 h after the last infusion. Plasma was separated by centrifugation immediately after collection and stored in capped vials at −80° C until assayed. Urine was collected at 6-h intervals and the pH was adjusted to 3–4 with ascorbic acid, and 20-ml aliquots were stored at −80° C for analysis.

CI-921 determinations. Total CI-921 concentrations were determined in duplicate 0.5-ml plasma samples by our previously published HPLC method [9]. This assay was accurate, with recoveries of 98.3%–106.6% over the range 0.05–20 μmol/l, and precise, with intra-assay coefficients of variation (CV) (n = 9) of less than 4.3% for the range 0.1–20 μmol/l. The minimal plasma concentration that could be measured with acceptable precision (i.e., CV < 10%) was 0.05 μmol/l; concentrations below this were regarded as zero, and concentrations greater than 20 μmol/l were diluted with blank plasma to within the assay range. Three spiked quality control samples (15, 1, and 0.1 μmol/l) were made up in blank plasma prior to the study, aliquoted into 2-ml samples, stored at −20° C, and included in each assay. After 9 months and 66 assays, the mean concentration (%CV) for each was 14.54 (3.9%), 1.01 (4.0%), and 0.095 (7.3%) μmol/l, with no apparent trend in these values.

A similar procedure was used for the determination of urinary CI-921, omitting the hexane wash and using an alternate internal standard, *N*,4-ethyl-5-methyl-9-[(2-me-

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Table 1. Patient details

Patient	Age/Sex	Weight (kg)	Tumor	Other drugs
001	56/F	75	Breast	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11
002	57/M	76	Pancreas	3, 8, 12, 13, 14
003	48/M	54.5	Melanoma	15
004	67/F	45.5	Melanoma	16, 17
005	47/M	79	NSCCL	6, 8, 14, 18, 19, 22
006	53/M	64	NSCCL	–
007	53/M	68	Stomach	6, 8
008	64/F	68	Breast	6, 10, 20
009	53/F	65.6	NSCCL	1, 18, 21, 23
010	70/M	58	NSCCL	8, 19, 24, 25
011	21/M	70.5	Melanoma	14, 22
012	65/M	56.5	NSCCL	–
013	57/M	106	NSCCL	19, 26
014	54/M	80	Head and Neck	27
015	57/M	62	SCCL	6
016	57/M	94	Melanoma	14

NSCCL, Non-small-cell carcinoma lung; SCCL, small-cell carcinoma lung
1, Hydrochlorthiazide/amiloride; 2, prazosin; 3, amitriptylline; 4, thiethylperazine; 5, nefopam; 6, triazolam; 7, "Slow K"; 8, morphine sulfate; 9, penicillin; 10, ampicillin; 11, ferrous sulfate; 12, triamterene/hydrochlorthiazide; 13, methyldopa; 14, dextropropoxyphene/paracetamol; 15, vitamin C; 16, promethiazine; 17, hydrocortisone; 18, prechlorperazine; 19, metoclopramide; 20, cloxacillin; 21, azatadine maleate; 22, naproxen; 23, paracetamol/codeine; 24, ibuprofen; 25, nifedipine; 26, pindolol; 27, glibenclamide

thoxy-4-methylsulfonyl-amino)phenyl-amino]-4-acridine-carboxamide, to avoid interference from other urinary compounds in the chromatographic separation. The urinary assay was less sensitive, with 0.1 μmol/l being the lowest concentration measurable with a CV of $< 10\%$.

Pharmacokinetic analysis. The slope (β) of the terminal linear portion of the log concentration-time profile was estimated by unweighted least-squares regression and the initial slope (α), from the method of residuals. The initial ($t_{½\alpha}$) and terminal ($t_{½\beta}$) half-lifes were then calculated from $\log_e 2$ divided by the appropriate slope. The area under the plasma concentration-time curve (AUC) and the area under the first moment of the concentration-time curve (AUMC) were determined using the trapezoidal rule when successive concentration values were increasing and the log trapezoidal rule when successive concentration values were decreasing after the maximum. Both were extrapolated to infinity by the addition of C_t/β to the former and C_t/β $(T_t + 1/\beta)$ to the latter, where C_t is the concentration at the last time point (T_t). The following model-independent pharmacokinetic parameters were calculated: total plasma clearance (CL = dose/AUC), the mean residence time of drug elimination (MRT = [AUMC/AUC] – T/2), and the apparent volume of distribution at steady state (V_{ss} = CL × MRT), where T is the time for this short constant-rate infusion [7, 14].

Plasma CI-921 concentrations greater than 0.05 μmol/l were detectable prior to the third infusion on two occasions and contributed to the AUC and AUMC for the third infusion. This contribution was estimated by substituting this C_t and a mean value for β (from the first and third infusion) in the "extrapolation to infinity" equations and subtracting this from the AUC and AUMC for the third infusion. The plasma concentration-time profiles were also tested by MKMODEL to determine whether a one- or two-compartment open model with zero-order input would provide the better fit [8].

Pharmacokinetic parameters from the first and third infusions were compared by the two-tailed Student's paired *t*-test. Correlations were assessed by Pearson's correlation coefficient (r_p) or by Spearman's rank correlation (r_s), where the variance of the *y* variate appeared to change with *x*. The relationship between the dose and the AUC and C_{max} was estimated by the unweighted least squares of the regression line passing through the origin. Differences in the daily excretion of unchanged drug were assessed by one-way analysis of variance.

Results

The pharmacokinetics of CI-921 were studied after 65 infusions in 16 patients. Plasma concentration-time profiles for the dose range 13–270 mg/m^2 were typically biphasic (Fig. 1). By 24 h postinfusion, plasma CI-921 concentrations had fallen below 0.05 μmol/l, except in two patients (013, course 3; 016, course 1) who received 216 mg/m^2. The modelling program indicated that the two-compartment rather than the one-compartment open model was the better fit for the concentration-time data in all cases. However, in several patients after high doses, a possible third phase in the elimination curve was apparent at 18–24 h.

The log concentration-time profiles after the day 1 and day 3 infusions of each course were similar and in many cases superimposable. There was no significant difference by the paired Student's *t*-test ($n = 32$) between the end of the infusion concentration (C_{max}), AUC, CL, V_{ss}, MRT, $t_{½\alpha}$, and $t_{½\beta}$ calculated for the day 1 and day 3 infusions. The ratios of the day 3/day 1 pharmacokinetic parameters at each dose level are given in Table 2. There was no obvious trend in these ratios with increasing dose.

The mean pharmacokinetic values calculated from the first and third infusions of each course are reported in Table 3 and the mean values at each dose level, in Table 4. There was a strong linear relationship between the dose

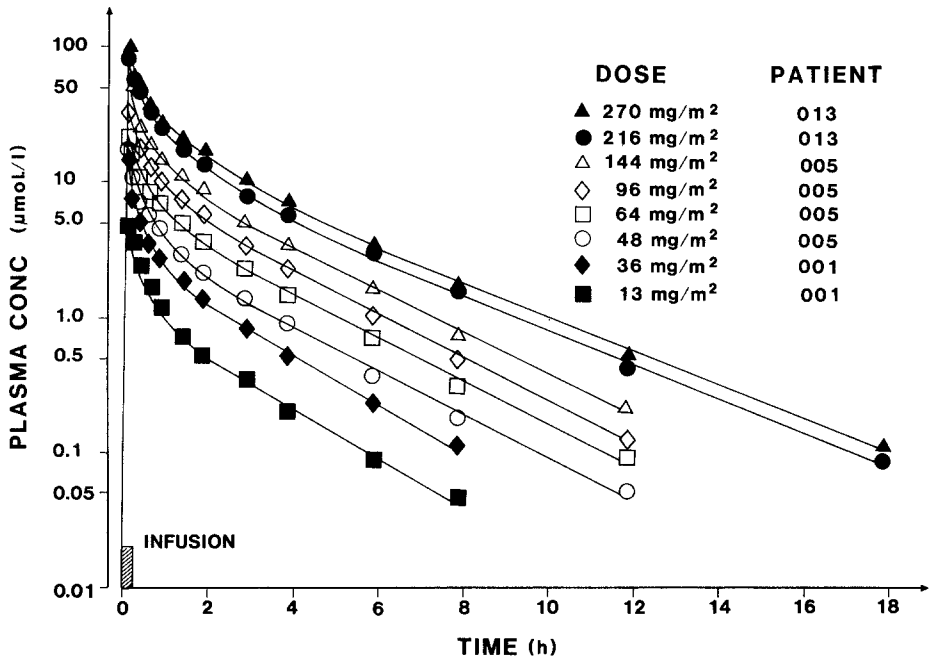

Fig. 1. Plasma CI-921 concentration-time profiles after the first infusion of 13 mg/m² (■) and of 36 mg/m² (◆) in patient 001; 48 (○), 64 (□), 96 (◇), and 144 mg/m² (△) in patient 005; and 216 (●) and 270 mg/m² (▲) in patient 013

Table 2. Mean ratios of day 3/day 1 pharmacokinetic parameters after the first and third infusions of a 3-day course with increasing dose

Dose	Courses/Patients	C_{max}	AUC	CL	V_{SS}	MRT	$t_{1/2\alpha}$	$t_{1/2\beta}$
13	2/2	1.19	0.96	1.06	0.92	0.89	0.76	0.84
36	3/3	1.03	0.97	1.05	0.84	0.81	0.85	0.75
48	4/4	1.06	1.10	0.92	0.97	1.07	1.15	1.18
64	3/3	1.13	1.01	0.99	0.99	1.01	0.96	1.10
96	3/3	1.00	0.89	1.16	1.21	1.05	0.92	1.19
144	4/4	1.14	0.98	1.04	1.04	1.01	0.89	1.11
216	10/7	1.00	1.02	0.98	1.01	1.04	1.18	1.27
270	2/2	0.97	1.02	1.15	1.00	0.87	0.87	0.74
	Mean	1.06	0.99	1.04	1.00	0.97	0.95	1.02
	% CV	7.50	6.10	7.90	10.60	10.10	15.40	20.80

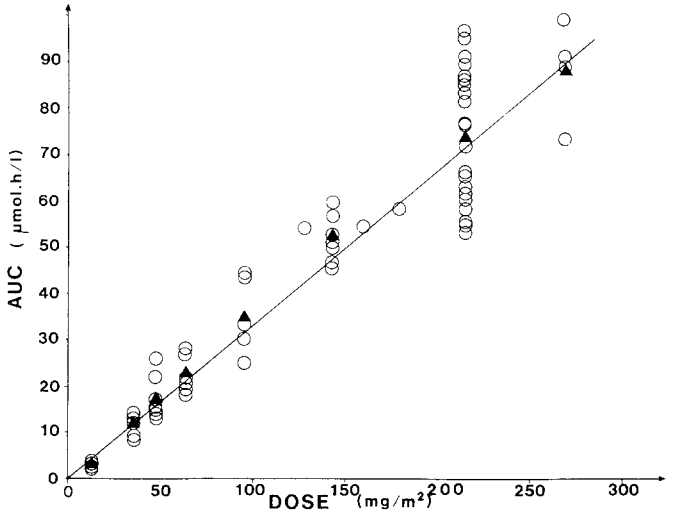

Fig. 2. Relationship between the dose and AUC. The *line* represents the least-squares linear regression through the origin ($y = 0.330x$). ▲, the mean AUC at each dose level

and AUC ($r_s = 0.953$, $P < 0.001$) over this dose range (Fig. 2). A similar relationship was also observed between the dose and C_{max} ($r_s = 0.949$, $P < 0.001$). Scatter diagrams of the relationships between the dose and the various pharmacokinetic parameters (V_{ss}, CL, MRT, and $t_{½\beta}$) are shown in Fig. 3 and 4. No strong correlations ($r > 0.5$) were observed between the dose and any of these parameters. Over the 20-fold dose range, 3-fold variations were obseved in the CL (94–290 ml/h per kg), V_{ss} (219–614 ml/kg), and MRT (1.1–3.5 h), and even greater variations in the $t_{½\beta}$ (1.1–5.0 h) (ranges from the 65 individual infusions). Large variations in these parameters were also observed within a single dose level (e.g., 216 mg/m²) as well as within individual patients at different dose levels. The variations in the relationship of the AUC with increasing dose within individual patients are shown in Fig. 5.

The urinary excretion of unchanged CI-921 was variable and low, with less than 1% (0.18–0.92%) of the total dose excreted within 24 h of the third infusion. Most of this appeared in the initial postinfusion sample, and by 18–24 h CI-921 concentrations were generally undetectable. Over this dose range, there was a weak linear correlation between the dose and the percentage excreted un-

Table 3. Mean CI-921 pharmacokinetic parameters calculated from the first and third infusions after different doses in all patients

Patient	Dose (mg/m^2)	C_{max} (μmol/l)	AUC (μmol/h per l)	CL (ml/h per kg)	V_{SS} (ml/kg)	MRT (h)	$t_{1/2\alpha}$ (h)	$t_{1/2\beta}$ (h)	UE** %
001	13	4.93	3.85	171	248	1.4	0.3	1.5	0.43
001	36	9.88	8.78	201	299	1.5	0.4	1.7	0.17
001	48	18.56	14.91	157	320	2.0	0.4	3.2	0.29
001	64	26.90	27.63	116	295	2.6	0.4	3.1	0.46
002	13	3.40	2.54	279	324	1.2	0.3	1.3	NA
003	36	10.26	13.94	166	309	1.9	0.5	1.7	NA
004	36	9.46	12.79	189	520	2.8	0.5	3.1	NA
005	48	13.78	14.30	174	348	2.0	0.4	2.1	0.53
005	64	18.35	21.14	154	308	2.0	0.4	2.0	0.45
005	96	29.44	31.88	152	311	2.0	0.4	2.0	0.49
005	144	50.00	51.26	141	289	2.1	0.4	2.4	0.57
005	180	49.00	56.50	150	365	2.4	0.5	3.1	0.66
005	216	60.67	65.88	165	317	1.9	0.55	2.9	0.53
006	48	18.17	23.94	120	367	3.1	0.5	3.5	NA
007	48	17.93	17.15	161	302	1.9	0.4	2.2	NA
008	64	22.00	19.19	180	320	1.8	0.4	2.1	0.39
008	96	33.77	29.32	179	340	1.9	0.4	2.1	0.46
008	144	65.58	52.68	155	302	1.9	0.3	2.6	0.67
009	96	39.57	44.35	126	245	1.9	0.5	2.5	0.34
009	129*	53.97	54.10	140	219	1.6	0.5	1.9	0.48
009	144*	56.24	57.08	149	246	1.7	0.4	1.9	
010	144	41.26	49.15	180	420	2.3	0.5	2.9	0.58
010	216	44.95	78.88	169	483	2.9	1.0	4.3	0.70
011	216*	55.43	55.14	220	328	1.5	0.5	1.8	0.54
012	216	61.59	61.70	214	404	1.9	0.5	2.6	0.64
013	270	81.33	95.02	116	257	2.2	0.5	2.5	0.80
013	216	68.72	86.53	104	253	2.4	0.5	2.7	0.92
013	216	66.80	92.84	97	236	2.5	0.6	3.4	0.75
014	270	83.07	81.27	136	307	2.0	0.5	3.8	0.18
014	216	59.12	59.61	149	280	1.9	0.4	2.2	0.32
014	216	65.62	59.21	151	255	1.7	0.4	2.1	0.47
015	216	73.78	84.15	160	315	2.0	0.6	3.1	0.54
015	216	84.66	93.08	150	307	2.1	0.6	3.8	0.72
016	216	66.37	74.23	135	318	2.6	0.6	4.1	0.53
Mean				158	319	2.1	0.5	2.6	0.52
n				34	34	34	34	34	28
SD				36	68	0.4	0.1	0.9	0.18
%CV				23	21	21	29	33	33

* Single infusion
** Percentage of dose excreted as unchanged drug in the urine (mean of 3 days). NA, not assayed
Doses were given in the order appearing in the Table

Table 4. Mean (SD) kinetic parameters at increasing i.v. doses

Dose (mg/m^2)	Infusion/ Patients	AUC (μmol/h per l)	C_{max} (μmol/l)	CL (ml/h per kg)	V_{SS} (ml/kg)	MRT (h)	$t_{1/2\alpha}$ (h)	$t_{1/2\beta}$ (h)
13	4/2	3.2 (0.9)	4.2 (1.1)	225 (76)	286 (54)	1.3 (0.1)	0.3 (0)	1.4 (0.1)
36	6/3	11.8 (2.7)	9.9 (0.4)	185 (18)	376 (124)	2.1 (0.7)	0.5 (0.1)	2.2 (0.8)
48	8/4	17.6 (4.4)	17.1 (2.2)	153 (23)	334 (29)	2.3 (0.6)	0.4 (0.1)	2.8 (0.7)
64	6/3	22.7 (4.4)	22.4 (4.3)	150 (32)	308 (13)	2.1 (0.4)	0.4 (0)	2.4 (0.6)
96	6/3	35.2 (6.6)	34.3 (4.2)	152 (22)	299 (40)	1.9 (0)	0.4 (0)	2.2 (0.2)
144	7/4	52.5 (3.3)	53.3 (10.3)	156 (17)	314 (74)	2.0 (0.2)	0.4 (0.1)	2.5 (0.4)
216	21/8	73.8 (14.1)	64.3 (10.2)	156 (38)	318 (72)	2.1 (0.4)	0.6 (0.2)	3.0 (0.8)
270	4/2	88.1 (9.7)	82.2 (1.2)	126 (14)	282 (35)	2.1 (0.1)	0.5 (0)	3.2 (0.9)

changed in the urine ($r_p = 0.3930$, $P = 0.0426$, 25 df). Over the 3-day course there was a small but significant increase in the percentage of unchanged drug excreted per day ($P = 0.0109$, by one-way analysis of variance). Overall mean (SD) values for days 1–3 were 0.45% (0.03%), 0.53% (0.05%), and 0.62% (0.05%).

Discussion

Over the dose range 13–270 mg/m^2, the plasma disposition of CI-921 was mainly biphasic during the 24 h after the infusion. The strong linear relationships between the dose and the AUC and C_{max} indicated linear kinetics over this dose range. In addition, the plot of AUC/dose vs dose

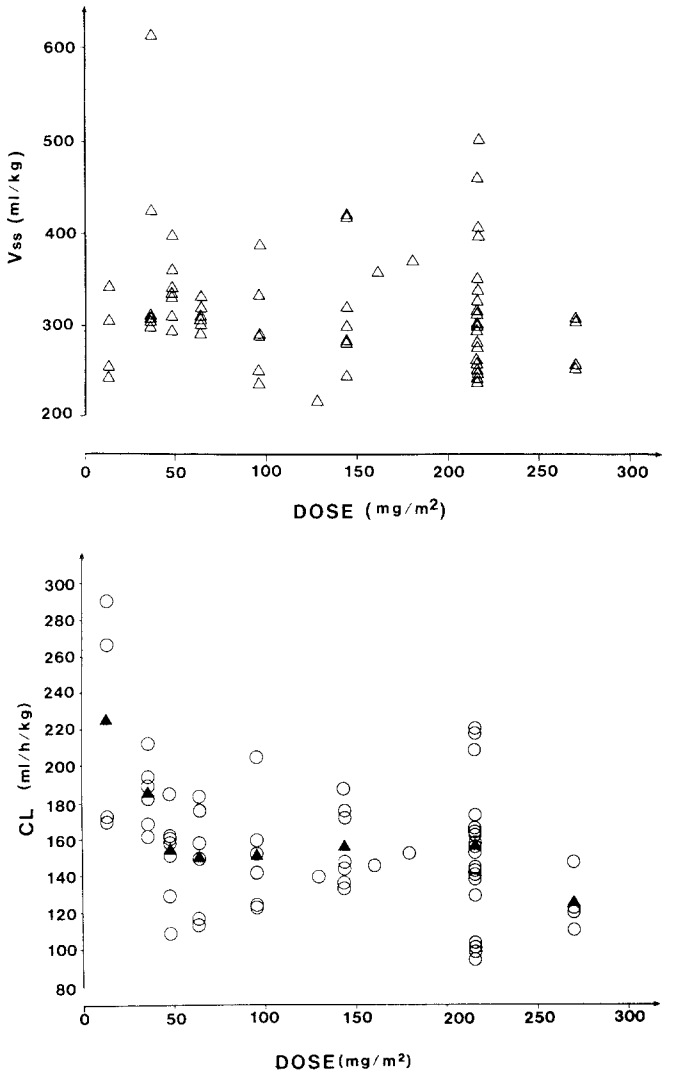

Fig. 3. Scatter diagrams of relationships between the dose and the CL and V_{ss}. ▲, the mean CL at each dose level

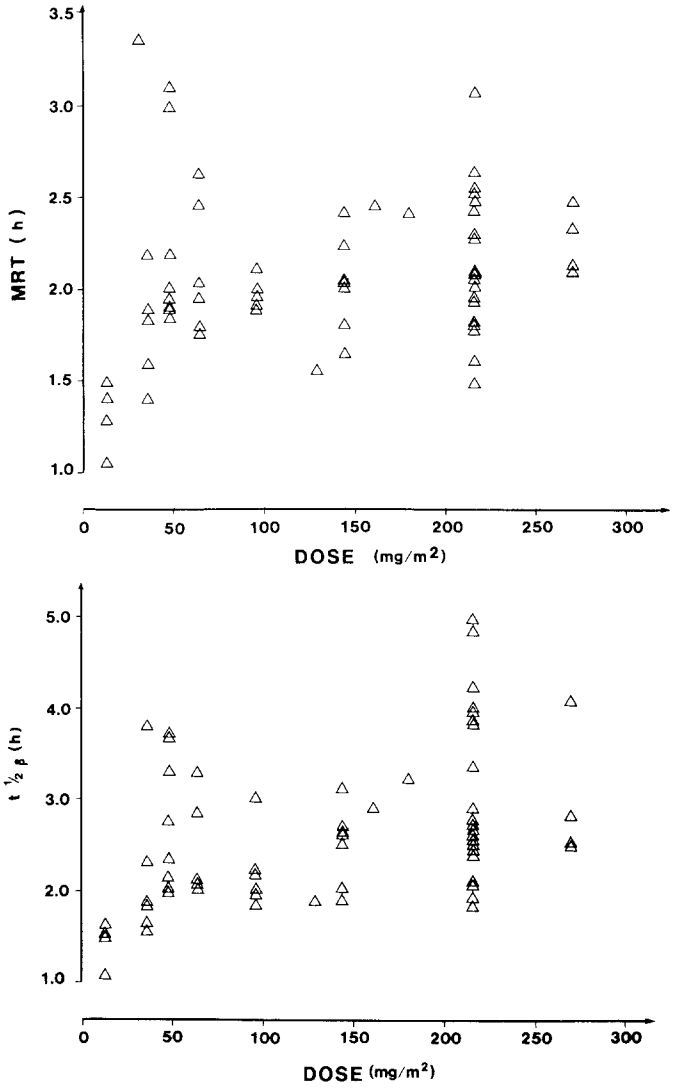

Fig. 4. Scatter diagrams of relationships between the dose and the MRT and $t_{½\beta}$

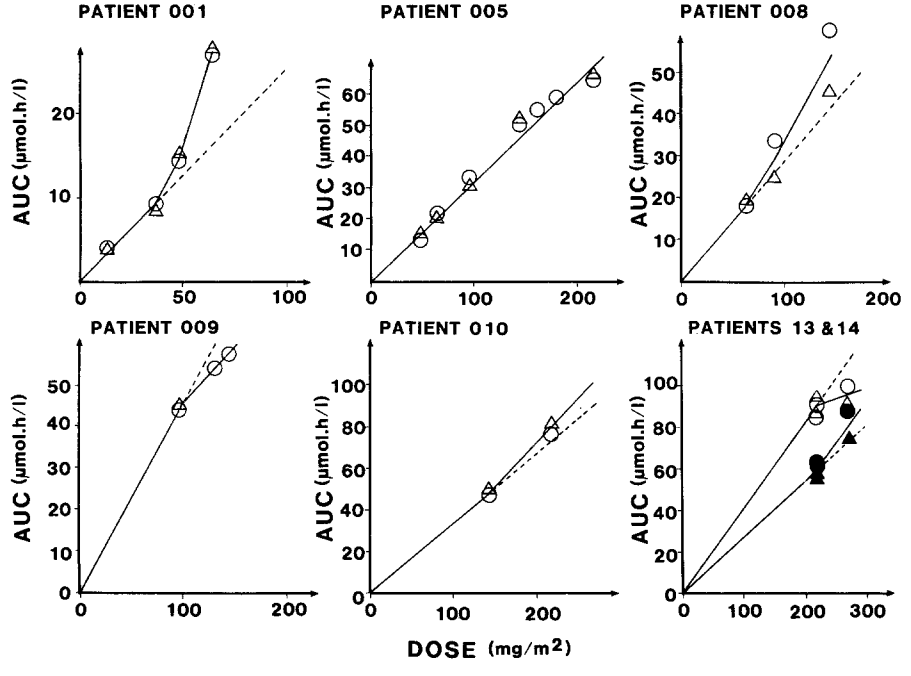

Fig. 5. Relationships between the dose and AUC in individual patients who received more than one course. ○, the first infusion; △, the third infusion of each course. The *dashed line* represents the predicted values for linear kinetics

and C_{max}/dose vs dose did not suggest any nonlinearity in the above relationships.

The pharmacokinetic parameters were mainly very similar between the first and third infusions of each course but very variable within patients at different dose levels and between patients at the same dose level. Much of this variation within and between patients might be due to the progression of the tumor and the general clinical condition of the patient. For example, patient 005 maintained a relatively constant CL over six escalating doses. He was fit and active throughout the study and survived 8 months after treatment. In contrast, the clinical condition of patient 001, whose CL decreased significantly over four doses (although with no apparent impairment of liver function), underwent marked deterioration during therapy, resulting in death 3 months later.

The urinary excretion was very low, suggesting hepatic metabolism as the principal pathway of elimination. Hepatobiliary excretion has proven to be the major route in the mouse and dog (personal communication), but its contribution in man has yet to be determined. Comparison of the mean value for total plasma clearance of CI-921 (158 ml/h per kg) with that for normal liver plasma flow rate (approximately 600 ml/h per kg) [3] have suggested that CI-921 has a relatively low hepatic extraction. Thus, its disappearance from plasma might be expected to depend on both intrinsic hepatic clearance and plasma protein binding [15]. CI-921 is very highly bound to plasma proteins (unpublished observations), and small binding changes might account for some of the variation in CL and V_{ss}.

The pharmacokinetics of CI-921 differ from those of its predecessor, amsacrine, given by a similar regimen (200 mg/m^2 by i.v. infusion on three consecutive days) [10]. The significant decrease in the CL and a prolongation of the $t_{½\beta}$ of amsacrine between the first and third infusions were not seen with CI-921. In addition. a larger percentage of amsacrine was excreted unchanged in the urine, as would be expected for a stronger base. Both compounds had a similar $t_{½\alpha}$, but CI-921 had a considerably (approximately 50%) shorter $t_{½\beta}$. Caution must be exercised in comparing the CL and V_{ss}, which are calculated from total plasma concentrations. These kinetic parameters are greatly influenced by the magnitude of the plasma protein binding of each compound. In our studies of the pharmacokinetics of amsacrine and CI-921 in the rabbit, we have observed that CI-921 was bound to a greater extent than amsacrine [12]. Using unbound concentrations, that study has indicated that CI-921 had a greater apparent volume of distribution and a greater intrinsic clearance than amsacrine [12]. Similarly in man, the plasma-unbound fraction of CI-921 was less than 0.3% (unpublished observations), compared with approximately 3% for amsacrine [13]. Using unbound concentrations to calculate kinetic parameters, the intrinsic CL of CI-921 in man would be in the region of sixfold, and the apparent volume of distribution, approximately two- to three-old that of amsacrine. Such altered kinetics may reflect a better tissue distribution for CI-921 than for amsacrine. The clinical effects of CI-921 are currently being investigated and will be published elsewhere.

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