

Phase I and Clinical Pharmacology Trial of 502U83 Using a Monthly Single Dose Schedule¹

Daniel D. Von Hoff,² John G. Kuhn, Kathleen A. Havlin, Anne-Marie Langevin, Thomas D. Brown, Geoffrey R. Weiss, Judy N. Turner, Joseph Purvis, V. Sol Lucas, Kenneth W. Bair, William Wargin, James Hubbell, Richard L. Tuttle, Jim M. Koeller, and Gregory L. Freeman

Division of Oncology, Department of Medicine and School of Pharmacy, University of Texas Health Science Center at San Antonio, San Antonio, Texas 78284-7884 [D. D. V. H., J. G. K., K. A. H., T. D. B., G. R. W., J. N. T., J. M. K., G. L. F.], and Burroughs Wellcome Co., Research Triangle Park, North Carolina 27709 [J. P., A-M. L., V. S. L., K. W. B., W. W., J. H., R. L. T.]

ABSTRACT

502U83 is an arylmethylaminopropanediol derivative exhibiting significant antineoplastic activity in a number of murine and human tumor models. In this Phase I trial, a 1-h or 4-h infusion of the agent was administered i.v. in 250 ml of 5% dextrose in water every 28 days. Fifty-three courses at doses of 25 to 2000 mg/m² were administered to 36 patients with refractory solid tumors. Prolongation of the PR, QRS, and QT intervals on electrocardiograms was dose limiting at 2000 mg/m². This prolongation appeared dose related and was reversible upon discontinuation of the infusion. No hematological toxicity was observed. Other toxicities included only sporadic and mild to moderate nausea and vomiting. No tumor responses were noted.

502U83 plasma concentrations were determined by high-pressure liquid chromatography. Complete pharmacokinetic profiles were obtained for 21 of the 36 patients. After infusion, plasma concentrations declined in a biexponential or in a triexponential manner with a harmonic mean terminal *t*_{1/2} of 8.83 h. Using a three-compartment model, the mean apparent volume of distribution at steady state and total-body clearance were 195 liters/m² and 42.5 liters/h/m², respectively, indicative of extensive tissue distribution. No correlation could be found between the pharmacokinetic parameters and prolongation of the cardiac conduction intervals. Because of the cardiac effects with the drug, the schedule of administration of 502U83 used in this study cannot be recommended.

INTRODUCTION

The group of molecules collectively known as AMAPs³ has shown a broad spectrum of antitumor activity in murine and human tumor systems. To explore the potential utility of this novel series, four of the congeners have been selected for clinical development on the basis of antitumor activity, physicochemical properties, and drug disposition differences. In this study, we report results of a Phase I trial with one of the congeners, 502U83.

Biophysical studies have shown that 502U83 (Fig. 1) is the most hydrophilic of the four clinical candidates and binds relatively weakly to DNA (1). However, the precise mechanism of action of 502U83 is unknown. Like the other congeners, it showed *in vitro* and *in vivo* activity against P388 leukemia (with a high percentage of long-term survivors), L1210 leukemia,

B16 melanoma, M5076 sarcoma, Lewis lung carcinoma and colon 38. It is active against P388 sublines that are resistant to mitoxantrone and actinomycin D but not against acridinyl anisidide or doxorubicin-resistant lines. It is orally active and produces regression of P388 implanted in the footpad. The agent also has activity against a variety of human tumor colony-forming units growing in soft agar, including breast, colon, non-small cell lung, and renal cell colony-forming units (2).

One of the most attractive features of 502U83 was that in animals it did not have any acute central nervous system effects that were noted with the other two congeners brought into clinical trials (crisnatol and A773U). Rodent lethality studies identified the single-dose LD₁₀ to be 81 mg/kg and the LD₉₀ as 119 mg/kg in the mouse; for rats, the doses were about 20% higher (3). In dogs, emesis was the only acute effect noted. Dose-related antiproliferative effects included hypocellular marrow, atrophic lymphoid tissue, and maturation arrest enteritis at peak plasma concentrations ranging from 7.3 to 17.3 µg/ml. Electrocardiograms performed on the dogs at nonmetagenic doses of 502U83 showed no significant changes. The human starting dose was 1/10 of the murine LD₁₀ adjusted on a surface area equivalence basis.

MATERIALS AND METHODS

Patient Selection. The clinical characteristics and diagnoses for patients in this trial are displayed in Table 1. Thirty-six patients were entered into the study. All patients had histologically documented advanced solid tumors, for which there were no forms of more effective therapy. Measurable or evaluable disease was not required for admission to the study. In compliance with institutional and federal guidelines, written informed consent was obtained from all patients. Patients were required to have adequate organ function, including the following: bone marrow: WBC, ≥3,000/mm³ (granulocytes, ≥1,500/mm³), platelets, ≥100,000/mm³, hemoglobin, ≥10 g/100 ml; hepatic: bilirubin, ≤2.5 mg/100 ml, serum glutamic oxaloacetic transaminase, ≤2.0 times normal, alkaline phosphatase, ≤2.0 times normal (higher values of serum glutamic oxaloacetic transaminase and alkaline phosphatase were allowed if due to patient's tumor), prothrombin time and partial thromboplastin time, normal; renal: normal urinalysis, creatinine, ≤2.0 mg/100 ml; cardiac: no history of recent myocardial infarction or uncontrolled arrhythmia; metabolic: normal electrolytes, including calcium, phosphorus, and uric acid, and blood glucose, <200 mg/100 ml. Patients were required to have a Karnofsky performance status of 60 or better and must have been off previous anticancer therapy for at least 3 wk (6 wk if the previous therapy was a nitrosourea or mitomycin C).

Treatment Plan. Patients were hospitalized for each dose of 502U83. The formulation of the drug for clinical use was supplied by Burroughs Wellcome Co. as a sterile powder in 100-mg vials. The vials were reconstituted with 10 ml of bacteriostatic water for injection. The solution was then passed through a 0.22-µm filter and further diluted in 250 ml of 5% dextrose in water. The drug was administered to patients through a free-flowing i.v. line, using an infusion pump over 1

Received 1/9/90; accepted 8/30/90.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked *advertisement* in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

¹ Supported by NIH Grant RR-01346, a grant from Burroughs Wellcome Co., a grant from the American Cancer Society (Clinical Oncology Career Development Award to G. R. W.), and the clinical and support services of Audie L. Murphy Memorial Veterans Administration Hospital, San Antonio, TX. G. L. F. is an established Investigator of the American Heart Association.

² To whom requests for reprints should be addressed, at Section of Drug Development, The University of Texas Health Science Center at San Antonio, 7703 Floyd Curl Drive, San Antonio, TX 78284-7884.

³ The abbreviations used are: AMAP, arylmethylaminopropanediol; LD₁₀, 10% lethal dose (LD₉₀ defined similarly); ECG, electrocardiogram; AUC, area under the curve; C_{max}, maximum concentration; HPLC, high-pressure liquid chromatography; V_{dss}, volume of distribution at steady state; CL, clearance; V_c, volume of distribution of the central compartment; MRT, mean residence time.

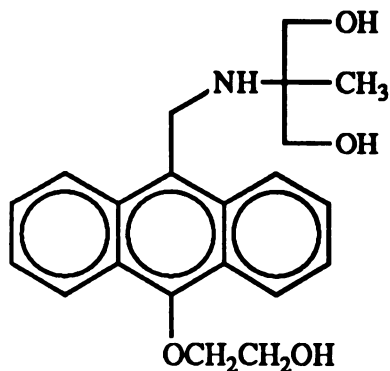


Fig. 1. Structure of 502U83.

Table 1 Patient characteristics

No. of patients (total)	36
Men	33
Women	3
Performance status, Karnofsky (no. of patients)	
Range	60–100
Median	70
100	2
90	6
80	10
70	7
60	11
Age (yr)	
Range	41–78
Median	64
Prior treatment (no. of patients)	
None	7
Radiation therapy only	4
Chemotherapy only	5
Chemotherapy and radiation therapy	20
Tumor types (no. of patients)	
Colon	9
Lung (non-small cell)	6
Unknown primary	6
Kidney	5
Breast	2
Head and neck	2
Prostate	2
Stomach	1
Hepatoma	1
Sarcoma	1
Testicular	1

Table 2 Dose escalation scheme

Dose (mg/m ²)	No. of patients	No. of courses
25	3	5
50	3	5
100	3	4
200	6	6
400	4	6
800	3	10
1200	3	3
1600	4	6
2000 (1-h infusion)	4	5
2000 (4-h infusion)	3	3

h (first 33 patients) or over 4 h (last 3 patients). If no tumor progression occurred, the patients were retreated every 28 days.

At the start of the study, all patients had a baseline 12-lead ECG as well as continuous ECG monitoring during the infusion. Because of prolongation of conduction intervals at doses ≥ 800 mg/m², each patient had a 12-lead ECG as a baseline, continuous ECG monitoring during the infusion, and a repeat 12-lead ECG at the end of infusion as well as during the infusion as indicated.

Doses were escalated by doubling the dose until a biological effect was seen, at which point they were increased by 50% until Grade 1 toxicity was noted. At that point the escalations were reduced to 33% (Table 2). At least three evaluable patients were entered at each dose level. The first patient at each level was observed for 4 wk. If toxicity was acceptable, two additional patients were entered. When a dose of 2000 mg/m² given as a 1-h infusion was reached, prolongation of the PR, QRS, and QT intervals became significant (15 to 71% increase). In an attempt to decrease this effect, three additional patients were treated at 2000 mg/m² using a 4-h infusion. There was no inpatient dose escalation.

Study Parameters. Baseline studies on all patients included history and physical examination, complete blood count, serum chemistries, prothrombin time, partial thromboplastin time, urinalysis, chest X-ray, ECG, and appropriate baseline scans or X-rays needed to measure tumor response. After treatment, patients were seen in the clinic weekly for 4 wk. At each visit, evaluations included history, physical examination, toxicity notation, complete blood counts, serum chemistries, prothrombin time, partial thromboplastin time, and urinalysis. In addition, studies for tumor measurement or evaluation were performed prior to each course. Standard response criteria and WHO toxicity criteria were used in the evaluation.

Termination of Study. Patients were taken off study after completion of follow-up evaluations if their disease was found to be progressing by Day 29 of any course. Patients were also free to terminate their participation in the study at any time.

Blood Sampling. Blood samples for pharmacokinetic studies were obtained via an indwelling i.v. heparin lock in the arm contralateral to the infusion line. Serial 8-ml specimens were obtained in EDTA tubes before infusion, 30 min (1, 2, and 4 h with the 4-h infusion) into infusion, and at the end of infusion. Postinfusion samples were collected 10, 20, 40, and 60 min and 1.5, 2, 4, 6, 8, 12, 24, and 48 h postinfusion. The samples were centrifuged, and the plasma was collected, flash frozen, and stored at -20°C in polyethylene tubes. A baseline urine specimen was obtained, and several urine samples were collected during and after infusion with the last collection period ending at 48 h. The total volume of each sample was recorded; the urine sample was shaken; and a 20-ml aliquot was removed, labeled, and stored at -20°C . The concentration of drug in each specimen was measured by HPLC.

HPLC Analysis. A reverse-phase HPLC method was developed for the analysis of 502U83 in plasma and urine samples. Samples (0.5 ml) were alkalized with 50 μl of 12 N NaOH and extracted with 5.0 ml of methyl *t*-butyl ether. The samples were then mixed on a multipurpose rotator (protected from light) for 10 min, and 4.5 ml of the organic layer were transferred to a 16- x 125-mm disposable glass tube. A volume of 50 μl of formic acid was added to ensure that 502U83 was in the salt form. The samples were evaporated to dryness at 40–60 $^{\circ}\text{C}$ under a stream of nitrogen. The extraction procedure yielded 90% recovery of 502U83 from plasma. The residue was reconstituted with 250 μl of mobile-phase HPLC consisting of HPLC-grade water, acetonitrile, and 0.1 M monobasic potassium phosphate (57:33:10). The HPLC system consisted of a pump (Model 950; Waters, Milford, MA), variable wavelength UV detector (Model 841; Waters), autosampler (Model 710B Wisp; Waters), and chromatography control module (LDC, Riviera Beach, FL). The elution system consisted of a 2-cm Pelliguard LC-8 guard column (Supelco, Bellefonte, PA) and a Spherisorb S-5 C6 HPLC column, 10 cm x 4.6 mm (Anspec, Ann Arbor, MI). The mobile phase was pumped at a flow rate of 2.0 ml/min, and the detector wavelength was 254 nm. The coefficient of variation for the assay was less than 4 to 11% over the linear range of the assay (0.03 to 15.0 $\mu\text{g/ml}$), and the lower limit of the assay was set at 30 ng/ml for a 1.0-ml sample.

Pharmacokinetic Analysis. The 502U83 plasma concentration-time data were analyzed using a 2- or 3-compartment model with zero-order infusion. Nonlinear least-squares regression analysis was performed using NONLIN (4) with a weighting function of 1/concentration. The estimates of the intercompartmental rate constants and the V_c were used to calculate the terminal-phase $t_{1/2}$, V_{dss} , AUC, and total-body CL. The C_{max} was the highest 502U83 plasma concentration observed

Table 3 Changes in QTc intervals in patients receiving 502U83

Patient	Infusion time (h)	Dose (mg/m ²)	QTc baseline (ms)	QTc at end of infusion (ms)	% of increase in QTc ^a
20	1.25	800	420	460	9.5
21 ^b	1.00	800	452	464	2.7
22 ^b	1.00	800	410	431	5.1
23 ^b	1.03	1200	406	470	15.8
24 ^b	1.08	1200	423	460	8.7
25	1.08	1200	396	422	6.6
26 ^b	1.05	1600	400	398	-0.5
27 ^b	1.00	1600	425	448	5.4
28	1.17	1600	406	ND1 ^c	
29	1.75	1600	420	636	51.4
30	— ^d	2000	416	ND2 ^c	
31 ^b	1.67	2000	415	713	71.8
32 ^b	1.00	2000	402	574	42.8
33	1.00	2000	456	528	15.8
34	4.00	2000	495	647	30.7
35 ^b	4.08	2000	420	494	17.6
36 ^b	3.92	2000	437	510	16.7

^a At end of infusion, compared with baseline.

^b Patients on whom pharmacokinetic studies were performed.

^c ND1, end of infusion ECG could not be found for review; ND2, infusion not completed secondary to gastrointestinal bleed, and patient did not have follow-up ECG.

^d —, patient did not complete infusion secondary to gastrointestinal bleed during infusion.

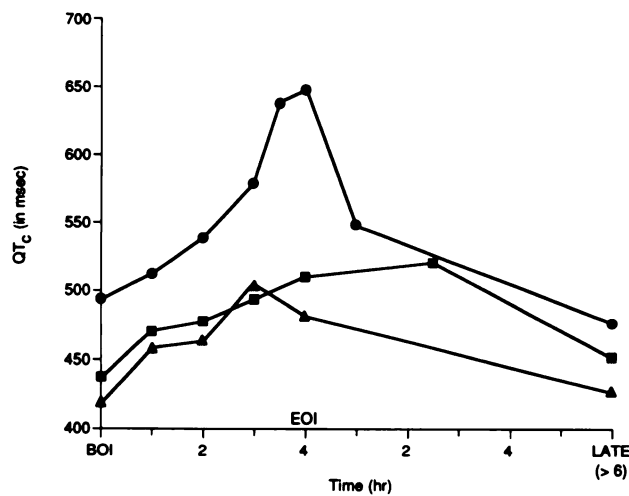


Fig. 2. QTc interval prolongation measured in three patients during infusion of 2000 mg/m² over 4 h. EOI, end of infusion.

during the infusion. The MRT was calculated by dividing the apparent V_{diss} by CL.

RESULTS

Thirty-six patients received a total of 53 courses of 502U83. One patient (patient 30 with hepatoma at 2000 mg/m²) had to

have the drug discontinued because of bleeding esophageal varices unrelated to 502U83. All other patients were evaluable for toxicity. Overall, 502U83 was well tolerated, and the toxicity which halted the trial was a consistent prolongation of conduction intervals found on electrocardiography.

Cardiac Conduction System Changes. No changes in cardiac conduction were noted up to doses of 800 mg/m². At that level, the 12-lead computerized ECG reader (Marquette, Marquette, WI) began to show prolongations in the PR, QRS, QT, and QTc (corrected QT) intervals. After that discovery, computerized ECGs were systematically performed pretreatment and at the end of infusion. All ECGs were reviewed by a reference cardiologist (G. L. F.). To quantify the ECG changes, the variations in the intervals were expressed as a maximum percentage of increase. Table 3 details the changes in the QTc intervals. The values detailed in Table 3 were then used to explore the relation between ECG changes, drug dose, and a variety of pharmacokinetic parameters. Since significant ECG interval changes were noted at doses ≥ 800 mg/m² and no significant changes were noted below that dose level, there was a suggestion of a greater prolongation of the QTc with increasing doses of 502U83 which, in turn, suggested the possibility of a peak plasma effect of 502U83. In an attempt to decrease a peak plasma level effect, a 4-h infusion of the agent was explored. As can be seen in Fig. 2 (and Table 3), patients receiving 2000 mg/m² over 4 h (with 12-lead ECGs performed hourly) still had QTc prolongations. The percentage of QTc prolonga-

Table 4 502U83 pharmacokinetic parameters (two compartment)

Patient	Infusion time (h)	Dose (mg/m ²)	$t_{1/2}$ (h)	C_{max} ($\mu\text{g/ml}$)	AUC (h \cdot $\mu\text{g/ml}$)	CL (liters/h/m ²)	V_c (liters/m ²)	V_{diss} (liters/m ²)	MRT (h)	I.E. ^a (h \cdot mg)
1	1.00	25	1.37	0.31	0.56	43.3	21.4	69.4	1.55	82.93
2	1.17	25	1.22	0.25	0.41	65.5	8.1	56.5	0.92	43.52
4	1.25	50	14.51 ^b	0.33	2.33	22.2 ^b	21.3 ^b	399.3 ^b	18.6 ^b	1869 ^b
5	1.08	50	1.05	0.64	0.93	55.6	11.3	40.3	0.75	60.46
8	1.17	100	1.83	1.04	1.67	61.2	8.9	86.4	1.45	287.10
9	1.00	100	1.97	0.70	1.91	55.5	33.0	109.0	2.08	424.32
Mean \pm SD			1.49 \pm 0.40 1.41 \pm 0.37 ^c						1.18 \pm 0.52 ^c	

^a I.E., index of exposure.

^b Excluded from mean.

^c Harmonic mean.

Table 5 502U83 pharmacokinetic parameters (three compartment) (1- and 4-h infusion schedule)

Patient	Infusion time (h)	Dose (mg/m ²)	<i>t</i> _{1/2β} (h)	<i>C</i> _{max} (μg/ml)	AUC (h·μg/ml)	CL (liters/h/m ²)	<i>V</i> _c (liters/m ²)	<i>V</i> _{ss} (liters/m ²)	MRT (h)
10	1.17	200	8.16	2.61	5.00	40.0	6.6	130.2	3.35
12	1.13	200	5.32	2.61	8.35	23.9	24.9	96.7	4.00
16	1.02	400	5.96	3.87	5.73	69.8	8.1	108.7	1.65
18	1.08	400	10.94	4.35	10.79	37.1	11.3	296.9	8.05
20	1.25	800	20.77	8.22	16.74	47.8	61.2	326.0	6.66
21	1.00	800	24.96	12.84	22.85	35.0	7.4	291.5	8.01
22	1.00	800	12.31	10.82	18.74	42.7	8.7	196.9	4.76
23	1.03	1200	10.07	14.40	23.60	50.8	12.2	222.5	4.36
24	1.08	1200	16.24	15.76	30.72	39.1	13.8	193.8	4.99
26	1.05	1600	5.63	26.92	46.52	34.4	5.1	105.6	3.12
27	1.00	1600	2.77	15.99	31.45	50.9	13.2	115.1	2.22
31	1.67	2000	13.43	12.05	44.86	44.6	57.4	226.2	4.62
32	1.00	2000	12.19	22.96	42.61	46.9	32.0	190.8	3.73
35	4.08	2000	23.64	11.35	54.22	32.9	15.8	169.5	5.15
36	3.92	2000	16.04	10.86	46.32	41.2	53.3	255.5	6.19
Mean ± SD			12.56 ± 6.75 8.83 ± 7.27 ^a			42.5 ± 10.50	22.10 ± 19.60	195.1 ± 74.93	3.94 ± 2.13 ^a

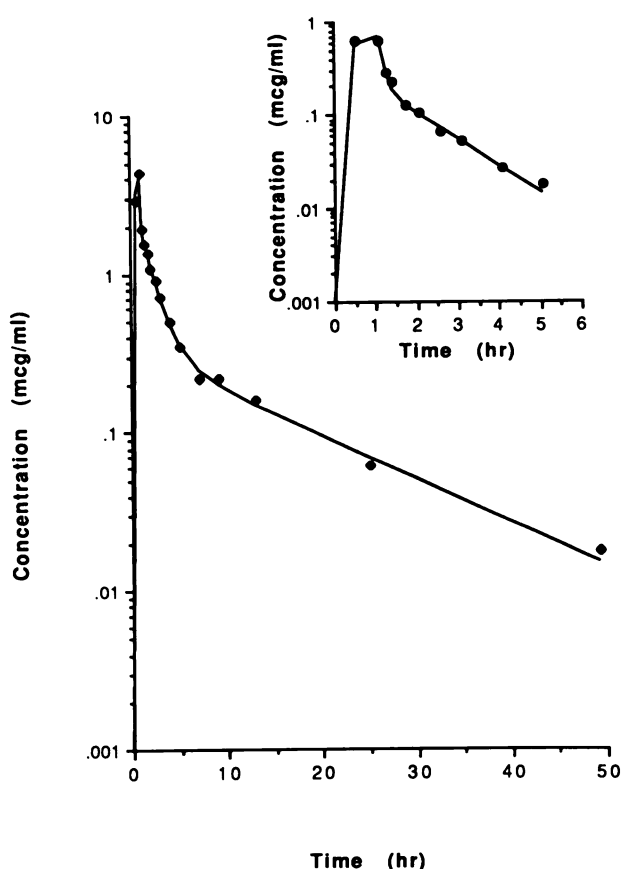
^a Harmonic mean.

Fig. 3. Representative plasma concentration versus time profiles for individual patients. Patient 18 receiving 400 mg/m² of 502U83. Inset is Patient 5 receiving 50 mg/m² of 502U83.

tions in the three patients at the end of the 4-h infusion were 16.7, 17.6, and 30.7%. These QTc prolongations were still significant enough for us to feel this 4-h schedule of administration was also not safe enough for patients.

The relation between the maximum QTc increase and a number of pharmacokinetic parameters was explored for the 10 patients receiving ≥ 800 mg/m² who had both pharmacokinetics performed and 12-lead ECG monitoring. There were no significant relations noted between the percentage of increase in QTc and the AUC, or MRT.

The PR and QRS intervals were also prolonged to a degree

similar to the QTc (data not shown). Thus, it appears that this agent has a global influence on transmembrane depolarization and repolarization in the heart. All of the interval prolongations were reversible. For example, in one patient, after a 4-h infusion, the QTc increased from a baseline of 495 ms to 647 ms at the end of the infusion. By 15 h after the infusion the QTc had returned to baseline (501 ms). Despite these prolongations no arrhythmias were noted, and no episodes of multifocal ventricular tachycardia ("torsades des pointes") occurred. Since, however, this had been previously described as happening for another chemotherapeutic agent which caused QTc prolongation, it was felt safest to abandon this schedule (5).

Serial serum potassium levels were obtained from patients at the highest dose level. There were no consistent changes in the potassium values to explain the ECG interval prolongations. However, prolongation of QT intervals was seen in the two patients who had potassium levels below 3 meq/liter. Some patients were receiving concomitant phenothiazines for nausea and vomiting, but the interval prolongations noted in these patients were no greater than the prolongations noted in patients not receiving concomitant phenothiazines.

Other Toxicities. The other toxicities noted with 502U83 included sporadic mild to moderate nausea and vomiting which did not appear dose related. Grade 1 leukopenia was noted in 2 patients at 2000 mg/m² (nadirs on Days 12 and 14, respectively). One patient had a minor extravasation of drug without consequence.

Antitumor Effects. No partial or complete tumor responses were noted in this Phase I study. Seven patients had stable disease for two to five monthly courses of therapy with all others having progressive disease after one course. The longest duration of stable disease (5 mo) was noted in a woman with renal cell carcinoma at the 800-mg/m² dose level.

Pharmacokinetics. The pharmacokinetic results are summarized in Tables 4 and 5. Plasma concentration versus time profiles for two representative individual patients are shown in Fig. 3. The plasma concentrations declined biexponentially and fit a 2-compartment model for the first nine patients up to and including doses of 100 mg/m² (see data for Patient 5, Fig. 3 inset). However, the data from the rest of the patients at >100 mg/m² were best fitted using a 3-compartment model (see data for Patient 18, Fig. 3). For these patients the harmonic mean terminal *t*_{1/2} was 8.83 h (see Table 5). The mean apparent volume of distribution at steady state was 195.1 liters/m², and the mean

total-body clearance was 42.5 liters/h/m². The increase in the AUC was proportional ($r^2 = 0.96$) to the increase in dose over the entire dosage range (50 to 2000 mg/m²).

DISCUSSION

This study reports on the second AMAP brought to clinical trial. The first AMAP in clinical trial was crisanol [2-[(6-chrysenylmethyl)amino]-2-methyl-1,3-propanediol] or BW77-0U82 mesylate. In Phase I clinical trials with that agent, reversible neurological toxicity was dose limiting (6). The agent is now undergoing Phase II trials at a dose of 2250 mg/m². In trials with that agent one patient developed reversible sinus node arrest. No other hints of cardiac effects with crisanol were noted, although preclinical studies had shown it to be a negative chronotope.

In the present study the maximum tolerated dose of 502U83 was determined to be 2000 mg/m². At that dose level, significant prolongation of PR, QRS, and QT was noted. Prolongation of the QT interval is a well-known effect of quinidine and other antiarrhythmic drugs such as procainamide and diisopyramide (7-9). Other drugs causing this effect include phenothiazines, tricyclic antidepressants, and amantadine overdoses (9, 10). Electrolyte disturbances such as hypokalemia and hypomagnesemia have also been reported to cause QT interval prolongation (7, 9). Of major interest is the prolongation of the QT interval described by Trump *et al.* (5) when they used the new antineoplastic agent, acodazole. The prolongation noted in their trial caused discontinuation of clinical trials with the agent, since one of their patients with the prolongation developed a ventricular tachycardia of the "torsades des pointes" type (11). As noted by Trump *et al.* there is an association between QT lengthening and life-threatening arrhythmias. This is particularly true for quinidine. Prolongations of the QT interval represent a longer period of ventricular repolarization, during which the ventricle is vulnerable to ventricular tachycardia or ventricular fibrillation resulting from single extrasystoles. While there is not a clear relation between the extent of QT prolongation and either the incidence of serious arrhythmias or the concentration of the offending agent, the degree of prolongation seen in these patients is clearly a cause for concern.

QT interval prolongations have been noted at the 4 highest doses (800, 1200, 1600, and 2000 mg/m²) of 502U83. Given the potential consequence of QT interval prolongation seen with other agents (*i.e.*, serious ventricular arrhythmias), we did not feel that further increases in doses of 502U83 on this schedule were justified.

It is of note that ECGs previously performed as part of the initial dog toxicology studies with 502U83 were within normal

limits. However, those ECG studies had been done at none-metogenic (low) doses of 502U83. After the cardiac effects were noted in patients, dogs were given a surface area equivalent dose to match the dose in humans. The dogs were so sensitive to other high-dose effects of the drug (*i.e.*, emesis) that meaningful ECGs could not be recorded.

Doses of 502U83 which do not produce QT interval prolongations are unlikely to achieve cytotoxic effects. Therefore, the use of a 1- or 4-h infusion cannot be recommended. Other Phase I trials, using 24- or 72-h infusions may provide a useful schedule for Phase II studies. Clearly, if schedule changes in the clinic do not allow bypassing of the conduction toxicity, development of a preclinical model will be necessary to try to find AMAP analogues which do not have this side effect.

ACKNOWLEDGMENTS

The authors thank Clair Waggoner and Julia Perkins for their excellent preparation of this manuscript as well as the nurses and personnel of the Special Diagnostic and Treatment Unit of the Audie Murphy VA Hospital.

REFERENCES

- Bair, K. W., Andrews, C. W., Tuttle, R. L., Knick, V. C., McKee, D. D., and Cory, M. Biophysical studies and murine antitumor activity of arylmethylaminopropanediols (AMAP), a new class of DNA binding drugs. *Proc. Am. Assoc. Cancer Res.*, 27: 424, 1986.
- Knick, V. C., Tuttle, R. L., Bair, K. W., and Von Hoff, D. D. Murine and human tumor stem cell activity of three candidate arylmethylaminopropanediols (AMAP). *Proc. Am. Assoc. Cancer Res.*, 27: 424, 1986.
- Everitt, B. J. M., Grebe, G., Mackars, A., Macklin, A. W., Whisnant, J. K., and Tuttle, R. L. Comparative pharmacology and toxicology of three arylmethylaminopropanediols (AMAP): BWA77U; BWA773U; and BWA502U. *Proc. Am. Assoc. Cancer Res.*, 27: 424, 1986.
- Metzler, C. M., Elfring, G. K., and McEwer, A. J. A package of computer programs for pharmacokinetic modeling. *Biometrics*, 30: 562-563, 1974.
- Trump, D. L., Tutsch, K. D., Willson, J. K., Remick, S., Simon, K., Alberti, D., Grem, J., Koeller, J., and Tormey, D. C. Phase I clinical and pharmacokinetic evaluation of acodazole (NSC 305884) an imidazoquinoline derivative with electrophysiological effects on the heart. *Cancer Res.*, 47: 3895-3900, 1987.
- Harman, G. S., Craig, J. B., Kuhn, J. G., Luther, S. G., Turner, J. N., Weiss, G. R., Tweedy, D. A., Koeller, J., Tuttle, R. L., Lucas, V. S., Wargin, W., Whisnant, J. K., and Von Hoff, D. D. Phase I and clinical pharmacology trial of crisanol (BWA770U mesylate) using a monthly single-dose schedule. *Cancer Res.*, 48: 4706-4710, 1988.
- Reynolds, E. W., and VanderArk, C. R. Quinidine syncope and the delayed repolarization syndromes. *Mod. Concepts Cardiovasc. Dis.*, 45: 117-121, 1976.
- Wald, R. W., Waxman, M. B., and Colman, J. M. Torsade de pointes ventricular tachycardia: a complication of disopyramide showed with quinidine. *J. Electrocardiol.*, 14: 301-308, 1981.
- Surawicz, B., Knoebel, G., and Suzanne, S. Long QT: good, bad, or indifferent? *J. Am. Coll. Cardiol.*, 4: 398-413, 1984.
- Sartori, M., Pratt, C. M., and Yay, J. B. Torsade de pointes. Malignant cardiac arrhythmia induced by amantadine poisoning. *Am. J. Med.*, 77: 388-391, 1984.
- Dessertenne, F. La tachycardia ventriculaire a deux foyes opposes variables. *Arch. Mal. Coeurvaiss.*, 59: 263-272, 1966.

Cancer Research

The Journal of Cancer Research (1916–1930) | The American Journal of Cancer (1931–1940)

Phase I and Clinical Pharmacology Trial of 502U83 Using a Monthly Single Dose Schedule

Daniel D. Von Hoff, John G. Kuhn, Kathleen A. Havlin, et al.

Cancer Res 1990;50:7496-7500.

Updated version Access the most recent version of this article at:
<http://cancerres.aacrjournals.org/content/50/23/7496>

E-mail alerts [Sign up to receive free email-alerts](#) related to this article or journal.

Reprints and Subscriptions To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions To request permission to re-use all or part of this article, use this link
<http://cancerres.aacrjournals.org/content/50/23/7496>.
Click on "Request Permissions" which will take you to the Copyright Clearance Center's (CCC) Rightslink site.