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Evidence of an absorption phase after short intravenous suramin infusions

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Summary. Suramin was given as an intravenous infusion to 16 cancer patients in a phase I trial. Individual pharmacokinetic parameters were calculated from a test dose given 1 week prior to the administration of a full-dose (350–700 mg/m^2) regimen of 1-h loading and maintenance infusions. A distribution phase of 3.8 h was found. Plasma suramin concentrations were noted to increase following cessation of the intravenous test infusion in eight subjects. A model is proposed in which high-capacity, low-affinity binding of suramin to a shallow compartment adjacent to the intravascular space occurs rapidly during infusion, followed by absorption back into the measured blood pool with binding to plasma albumin. Despite the observable presence of this postinfusion peak shortly after the cessation of the brief suramin infusion, the pharmacokinetics of suramin were best characterized by a traditional two-compartment model. The dose-adjusted area under the concentration-time curve (AUC) increased with dose, supporting a hypothesis of sustained absorption of suramin to vascular endothelium but also raising the possibility of dose-dependent clearance.

Introduction

Suramin is a polysulfonated naphthylurea that is undergoing Phase I and II trials as an antineoplastic drug (Fig. 1). It has been used extensively for the treatment of trypanosomiasis and onchocerciasis [19, 20] and was evaluated in the early 1980s as a possible treatment for human immunodeficiency virus (HIV) infections [3, 14]. Results of phase I and II cancer trials suggest a therapeutic benefit in patients receiving suramin for the treatment of hormone-refractory prostate carcinoma [17] or non-Hodgkin's lymphoma [3]. Undesirable toxicities of lethargy, peripheral neuropathy, and rare cases of Guillain-Barré syndrome have been reported as dose-limiting effects during extended suramin infusions and may define the maximal tolerated concentration of suramin given by this route [13, 17].

Several oncology applications of suramin studied to date at NCI-sponsored sites have used a continuous infusion of drug to establish a target concentration. Initially reported biexponential elimination with half-lives of 2 days and 20–50 days for suramin suggested that a regimen of short intravenous loading and maintenance infusions would permit shorter hospital stays and achieve target concentrations faster than would a continuous infusion [4]. Whereas 200-mg intravenous test doses of suramin have been given by other investigators in anticipation of hypersensitivity reactions, we sought to determine the pharmacokinetics of a test dose to provide adaptive control of subsequent full-dose therapy [8, 16]. The 16 patients reported on herein are part of a continuing phase I trial of suramin that continues to accrue subjects. This report addresses our findings of apparent dose-dependent changes in the plasma suramin concentration-time curve (AUC) and of an unusual peaking of suramin concentrations after the end of the infusion.

Patients and methods

Patient selection. A total of 16 subjects enrolled into the phase I trial of suramin at the University of Wisconsin Clinical Cancer Center underwent pharmacokinetic sampling. Patients eligible for this trial had histologically proven advanced malignancies that were not amenable to curative therapy. Primary sites included 11 patients with prostate carcinoma, 2 with renal-cell carcinoma, and 1 each with melanoma, pheochromocytoma, and adrenal carcinoma. All were men aged a median of 63 years (range, 38–77 years; Table 1).

Drug administration and sampling. Patients were admitted to the University of Wisconsin Hospital General Clinical Research Center (GCRC) at 1 week prior to full-dose therapy. The 200-mg intravenous test dose of suramin in 100 ml normal saline was infused over 1 h into a central or

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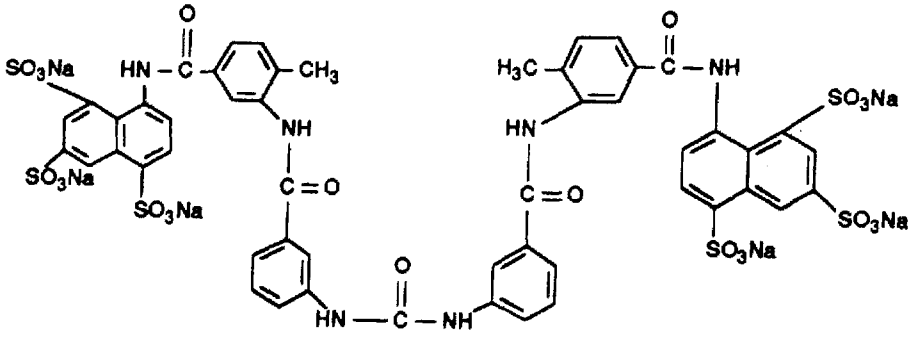

Fig. 1. Chemical structure of sodium suramin

peripheral vein. Heparinized venous blood samples were collected at the beginning, midpoint, and end of the infusion and at 0.25, 0.5, 1, 2, 4, 24, 48, 72, and 168 h after the end of the infusion. Test-dose sampling times were modified slightly in patients 5–16 to accommodate evidence of the then unexpected distribution phase seen in the first 4 subjects (0.5-h sample dropped; 10-h sample added). Blood samples could be drawn from the site of infusion no earlier than 2 h after the end of the infusion. Patients were discharged after the 72-h blood collection and were admitted at 1 week after the test dose for administration of the full-dose regimen. The test dose was increased as indicated in Table 1 when nonproportionality of test doses became apparent in the first six subjects. The suramin regimen instituted at 1 week after the test dose consisted of 1-h intravenous loading infusions of 700 mg/m^2 on days 1, 3, 5, 8, and 15, followed by weekly 1-h infusions thereafter. This initial dosing scheme was based on clearance and distribution volumes derived from data reported by Collins et al. [4].

Suramin assay. Plasma suramin concentrations were assayed by a reverse-phase ion-pairing high-performance liquid chromatography (HPLC) method ([12, 18]; Malspeis, unpublished data). After the addition of 20 μg Congo red as the internal standard, 200-μl aliquots of plasma were extracted twice with 100 μl 0.5 M *t*-butylammonium chloride (TBACl) and 1 ml acetonitrile to precipitate protein. Supernatant fractions were pooled and evaporated to dryness under nitrogen, followed by dissolution in 0.5–1 ml mobile phase for HPLC analysis. The isocratic mobile phase of 60:40 (v/v) 5 mM ammonium acetate/acetonitrile with 2 mM of the ion-pairing reagent TBACl was pumped at 1 ml/min through a NovaPak 4-μm C_{18} RadialPak 8 × 10 cartridge (Waters Associates). UV absorbance was measured at 238 nm.

The standard curve for suramin in plasma was linear from 2 to 500 μg/ml, with absolute recovery from plasma being determined to be 84%, and 104% when assessed by standard addition. The intraday variability of the assay from 5 to 500 μg/ml was <5%, with the interday variability over 3 weeks ranging from 4.3% (400 mg/l) to 8.6% (5 mg/l).

Pharmacokinetic calculations. Pharmacokinetic parameters associated with the test and full doses of suramin were estimated using the ADAPT II program [7]. In addition to the use of standard two- and three-compartment pharmacokinetic models, another model was developed that incorporated instantaneous adsorption of infused suramin to another "com-

Table 1. Subjects' characteristics and suramin test-dose findings

Subject	Test dose (mg/m^2)	Normalized AUC $\left(\frac{\text{mg h/l}^{-1}}{\text{mg/m}^2}\right)$	Suramin concentration (mg/l)	
			End of infusion	Maximum post-infusion[a]
1	121	10.3	44.2	61.0 (0.5)
2	92	8.5	29.8	29.8 (0.5)
3	114	7.3[b]	27.7	30.8 (0.5)
4	96	9.7	45.4	51.5 (0.25)
5	95	9.5	34.8	42.1 (0.25)
6	96	8.1	33.0	36.9 (0.25)
	Mean ± SD	9.2 ± 0.9 (n = 5)	35.8 ± 7.4 (n = 6)	
7	698	12.4	221.4	248.0 (0.25)
8	700	13.2	226.6[c]	–
9	700	13.8	257.9	320.0 (0.25)
	Mean ± SD	13.1 ± 0.7	235.3 ± 19.7	
10	412	14.8	186.7	–
11	330	16.4	159.0	–
12	317	13.6	140.6	–
13	333	11.3	130.5	143.0 (0.25)
14	321	17.5	164.0	164.4 (0.25)
15	347	15.1	168.2	–
16	291	10.8	115.9	–
	Mean ± SD	14.2 ± 2.5	152.1 ± 24.3	

[a] Values in parentheses represent the time of the postinfusion peak, if seen

[b] Sample collection for subject 3 was made only through 144 h; all other AUC intervals are 0–168 h

[c] Subject 8 received the test dose over 4 h instead of 1 h

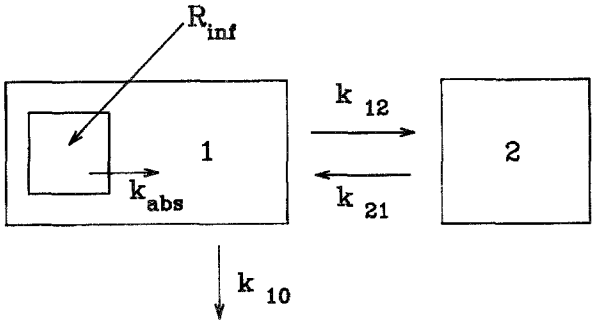

Fig. 2. Two-compartment model with infusion into another, shallow compartment from which drug is absorbed into the sampled compartment (*1*)

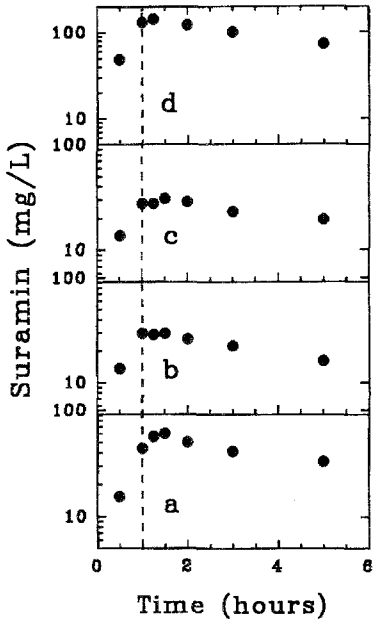

Fig. 3. Plot of plasma suramin concentrations over the first 6 h following test-dose infusion. *a*, Subject 1; *b*, subject 2; *c*, subject 3; *d*, subject 10. The *vertical dashed line* represents the end of the 1-h infusion

partment," followed by first-order absorption back into the central compartment (Fig. 2). This model was used to evaluate the rise or plateau of plasma suramin concentrations seen after the cessation of several suramin infusions in eight patients.

Model variance was estimated using concentration-dependent and -independent parameters [16]. The maximal likelihood estimator was used in all cases to approximate pharmacokinetic and variance parameters. Selection of the optimal model (two compartments with absorption versus two or three compartments, simple infusion) was made by choosing the model that minimized the Akaike Information Criterion (AIC) [1].

The AUC was calculated by the trapezoidal method over the interval 0–168 h. The 168-h time point represented the time of the therapeutic dose of suramin. Patient 3 received his test dose late, resulting in only a 0- to 144-h sample collection. The AUC was normalized to dose by dividing the AUC value by the test-dose amount.

Results

Test doses were well tolerated by all patients, although a nonpruitic erythematous rash was commonly observed. Table 1 presents the normalized AUC determined for each patient and indicates whether a post-infusion peak was

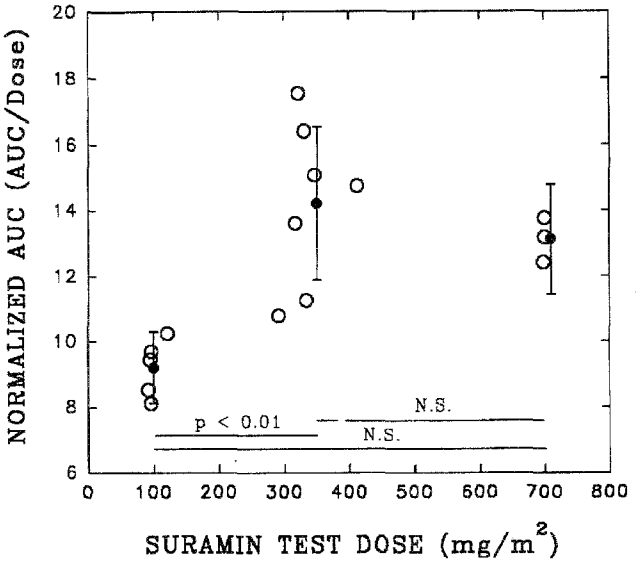

Fig. 4. Plot of dose-adjusted suramin AUC against dose. Error bars indicate mean values and 95% confidence intervals

seen. Figure 3 presents the plasma suramin concentrations measured during and after the test-dose infusion for four patients, demonstrating the unusual postinfusion peak.

Based on the AIC, a two-compartment model yielded the best fit for test-dose data in all but one subject. A two-compartment model with absorption improved the fit for patient 5. No benefit was found by fitting data to a standard three-compartment model. The central distribution volume and distribution clearance for suramin estimated from the test doses were 2.40 ± 0.47 l/m^2 and 0.273 ± 0.154 l h^{-1} m^2, respectively. These data correspond to a distribution half-life of 3.8 h for suramin.

Figure 4 illustrates the change observed in the dose-adjusted AUC with the delivered test dose. Patients were grouped by the size of their test dose (200 mg, 250–350 mg/m^2, 650–700 mg/m^2) for Kruskal-Wallis rank-sum tests of differences. Only the difference between the low and intermediate dose levels was significant ($P < 0.01$). The data on patient 3, for whom sampling was extended to only 144 h, is not included in Fig. 4. There was no statistically significant difference between the normalized AUC of the lowest and highest test doses as determined by the three-way Kruskal-Wallis test, but the power to detect a difference with only three points at the higher dose is low.

Discussion

The postinfusion peak in plasma suramin concentrations seen in half of our patients was very unusual. Plasma suramin concentrations should fall after the cessation of the intravenous infusion rather than climbing or remaining relatively constant for up to 1 h. This peaking is similar to the concentration-time curve expected from infusion into an extravascular space such as muscle or subcutaneous tissue. Suramin test-dose data in this trial were best fit by a standard biexponential model, although other researchers

have documented a terminal half-life of 30–50 days for suramin [6, 16]. Our evaluation of a triexponential model was used with little expectation of benefit, since the 7-day sampling period available before the therapeutic dose was barely sufficient for characterization of the reported 2-day intermediate half-life and could not incorporate the 50-day terminal half-life. Extended sampling following the cessation of therapeutic doses of suramin in these patients may corroborate the extended half-life of suramin reported by other investigators.

Our explanation of the postinfusion increase in suramin concentration incorporates high-capacity, low-affinity binding of suramin to sites on vascular endothelium. Persistent adsorption of suramin to vascular endothelium would decrease the AUC measured over the 7-day sampling period. If these binding sites were saturable, the lower AUC determined following small test doses would result in apparent nonlinear clearance as compared with larger doses in which the delivered dose is much larger in relation to the amount of drug that is adsorbed to the endothelium. In our series of patients, the clearance was noted to decrease as the dose was increased from 100 to 350 mg/m^2 in measurements obtained over the 7-day period following the infusion. Visual inspection of Fig. 4 suggests that the normalized AUC and, therefore, the clearance of the 100- and 700-mg/m^2 groups are also different. The lack of significant difference arises from the low power of detection due to the small number of patients receiving 700 mg/m^2.

The nonproportionately low AUC found with lower test doses concurs with our preliminary findings of dose-normalized AUC following the fifth therapeutic dose of suramin (data not shown). We have not disproven true nonlinear clearance of suramin. It is possible that the clearance of suramin does decrease with increasing doses. We doubt that this possibility is true, since in Table 1 and Fig. 4, there is no apparent change in clearance as the test dose is raised from 350 to 700 mg/m^2. Also, although limited by the availability of early samples, we found a postinfusion peak in several patients. This argues for a source of drug that can be returned to the central compartment to be measured. An incomplete return of suramin from these proposed binding sites during the 7-day sampling period would explain the unexpectedly low AUC obtained, regardless of whether a postinfusion peak was seen.

Suramin is known to bind to various heparin-binding sites, including epidermal, insulin, and tumor growth-factor receptors [10, 11]. In an evaluation of the bioavailability of the low-molecular-weight (LMW) heparin CY 216, Harenberg et al. [9] demonstrated that the AUC (antiXa units h ml^{-1}) determined following a 7,500-unit dose was 50% lower than expected as compared with the AUC observed after an 18,750-unit dose [9]. Thus, the apparent clearance of the low-dose heparin was comparatively lower for high doses, similar to our findings for suramin. In contrast, Bratt and colleagues [2] found no difference in the heparin AUC (expressed as antiXa units) with changes in LMW heparin. However, their selection of doses (40 and 60 units/kg) was lower and more narrow than those tested by Harenberg et al.

Using a bioassay of heparin, DeSwart et al. [6] demonstrated a convex curve in semilogarithmic plots of heparin elimination that were optimally characterized by parallel linear and saturable pathways. Our attempts to fit our suramin data to such a model were unsuccessful. The computer program was unable to fit the data due to inadequate data points. We plan to try mixed-effects modeling of our pooled data to evaluate further the possibility of saturable elimination or binding of suramin.

A potential drug interaction may arise between suramin and heparin if both drugs indeed compete for similar binding sites. Suramin may displace heparin from nonspecific binding sites, leading to an increased risk of bleeding. The eighth patient in our series expired with massive gastrointestinal bleeding [15]. He was not receiving heparin infusions and did not have an elevated activated partial thromboplastin time (APTT) at the time of his death. No direct evidence exists to demonstrate a drug interaction between suramin and heparin, but such an evaluation would appear prudent.

This report of a short distribution phase for suramin concurs with other recent publications [5, 16]. Our initial sampling schedule was not optimal for characterization of the distribution phase of 3.8 h, and it required modification by shifting away from the end of the infusion in subjects 5–16. Although this modification decreased our ability to characterize the postinfusion peak of suramin, a postinfusion peak was nevertheless seen at 15 min after the cessation of the infusion in 8 of the 16 subjects. The primary impact of this distribution phase is in the design of loading regimens to establish target concentrations. As might be expected from the extensive protein binding of suramin (>99.7%), its central distribution volume approximates that of plasma. In addition to limiting the size or rate of suramin infusions, these findings argue that suramin may be displaced by other highly protein-bound drugs that may lead to potentially harmful increases in free suramin concentrations. No study is yet under way to evaluate the effect of protein-binding drug interactions on suramin, but such investigations would also be prudent.

Our preliminary evidence indicates that steady-state distribution-volume and systemic clearance values calculated from test-dose data are subject to extreme error due to the unexpectedly low AUC seen with the smaller doses and to the short (7-day) sampling period. We are continuing our evaluation of 350-mg/m^2 test doses for prediction of subsequent suramin dosing needs.

In summary, suramin demonstrates a distribution half-life of 3.8 h. The pharmacokinetics of suramin after low-dose, short intravenous infusions are characterized by an unusual postinfusion peak and by dose-dependent changes in AUC. The findings are compatible with a model in which suramin binds rapidly with low affinity to a shallow depot compartment, possibly vascular epithelium, during the infusion. In this model, the suramin is then released back into the blood to yield a postinfusion peak. This may lead to inappropriately high estimations of systemic clearance from single-dose data. Drug interactions with heparin and highly protein-bound drugs are possible with suramin and should be evaluated.

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