Use of Adaptive Control with Feedback to Individualize Suramin Dosing

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ABSTRACT

Suramin is the first putative growth factor inhibitor in clinical trial that has demonstrated antitumor activity. Administration of suramin is complicated by a narrow therapeutic index and significant interpatient variability of measured pharmacokinetic parameters. Because both antitumor response and dose-limiting toxicities are related to plasma suramin concentration profiles, individualized dose schedules are required for optimal administration of the compound. In this report, the use of optimal sampling theory to derive sparse data monitoring and control strategies for use with suramin is described. A fixed rate continuous infusion schedule was used in seven patients, and the time to peak concentration (280-300 µg/ml) ranged from 7-21 days (mean, 13.2 days) with a decline to 150 µg/ml in 3-22 days (mean, 11 days). An initial population pharmacokinetic model was fit using a maximum likelihood algorithm. The mean volume of the central compartment was 45.2 ± 6.7 liters/m², volume of the peripheral compartment 10.6 ± 1.4 liters/m², distributional half-life 25 ± 5.4 h, and elimination half-life 29.7 ± 6.9 h. The terminal half-life was shorter than previously reported. These parameters were used as the initial population model for an iterative 2-stage analysis. The resulting distributional half-life of 22.3 ± 2.7 h and elimination half-life of 28.2 ± 5.0 h were similar, reflecting the intensive sampling. The iterative 2-stage analysis model was then used to determine the optimal sampling times and to simulate 20 data sets for a protocol designed to maintain plasma concentrations in a defined concentration range. This strategy is currently under investigation in phase I clinical trials.

INTRODUCTION

Suramin is a polysulfonated naphthylurea that is undergoing extensive clinical evaluation as an anticancer agent. This evaluation is based on its ability to inhibit growth factor binding to receptors, its toxic effects on adrenocortical tissue, and its demonstrated activity against a variety of human tumor-derived cell lines in vitro (1). Antitumor activity of suramin has been noted in patients with prostatic carcinoma (2), Kaposi’s sarcoma (3), renal cell carcinoma, and lymphoma (4). Suramin has several unique dose-limiting toxicities including a peripheral neuropathy that can progress to a Guillain-Barre syndrome (5), coagulopathy (6), vortex keratopathy (7), and increased risk of coagulation (8). The compound has also demonstrated activity against a variety of human tumor-derived cell lines in vitro (1). Antitumor activity of suramin has been noted in patients with prostatic carcinoma (2), Kaposi’s sarcoma (3), renal cell carcinoma, and lymphoma (4). Suramin has several unique dose-limiting toxicities including a peripheral neuropathy that can progress to a Guillain-Barre syndrome (5), coagulopathy (6), vortex keratopathy (7), and increased risk of infection despite normal granulocyte counts (2, 8). Clinical use of the compound is complicated by a narrow therapeutic window, suggested by data from phase I investigations, in which no responses were seen if peak plasma concentrations remained <200 µg/ml, while toxicities became prohibitive as concentrations exceeded 300 µg/ml (4, 5). As a result, careful monitoring of plasma concentrations is likely to be an essential component of therapy with this agent (9).

The initial clinical trials of suramin used a weekly dose schedule which proved to be too toxic. In subsequent studies, a continuous infusion of suramin was administered until plasma concentrations reached 280-300 µg/ml. Once achieved, therapy was stopped and the patient evaluated for response. Because of significant interpatient variability in plasma suramin concentrations, dose rates were adjusted weekly on the basis of a nomogram (10). The median time to achieve a therapeutic concentration using this schedule ranged from 1-4 weeks (4). Treatment was planned at 10-12 weeks in responding patients. This was based on the 52-day plasma suramin half-life observed in patients with AIDS who were treated using a weekly schedule (11, 12).

Our initial investigations, using a fixed rate continuous infusion, also showed significant interpatient variability (vide infra). Two of the first four patients achieved concentrations in the therapeutic range prior to the scheduled day 14 sampling and dose adjustment interval. In addition, we observed a more rapid decline to potentially subtherapeutic plasma concentrations than was anticipated on the basis of published half-life values. Of greatest concern was the absence of antitumor activity in the first nine patients treated. Inadequate exposure to suramin was postulated as one possible cause. The observed interpatient variability, narrow therapeutic window, and lack of therapeutic effect suggested the need for individualized dosing regimens based on pharmacokinetic parameters measured for each patient. This prompted the development of the adaptive control strategy reported herein (13).

The approach utilizes both previously derived population data and concentrations determined prospectively in an individual patient. It can permit concentrations to be maintained in a defined range. Data from individual patients were first fit using a maximum likelihood technique to determine the mean and SD for the pharmacokinetic parameters. This initial population pharmacokinetic model requires full data sets for each patient. The derived model estimates were then re-fit using an It2S Bayesian approach to refine the model. The model is constantly updated by repeating the process as more data become available.

The more data included for an individual patient, the less attention is paid to the population parameters. Once derived, the It2S parameters were used to determine a LSS that would include the most informative or “optimal sampling” times to measure plasma concentration of suramin in individual patients. Finally, the derived Bayesian algorithm was combined with a limited number of plasma samples to perform simulatio
tions designed to predict the effect of different dosage regimens for individual patients (14).

MATERIALS AND METHODS

The study population consisted of seven patients with bidimensionally measurable, hormone-refractory, metastatic, prostatic adenocarcinoma that was histologically confirmed by the Department of Pathology, Memorial Sloan-Kettering Cancer Center, New York, NY. All patients were treated on Cancer Therapy Evaluation Program Protocol T89–84 (phase II trial of suramin in hormone-refractory prostatic cancer). Entry requirements included a Karnofsky performance status ≥50, adequate hematomatologic reserve (WBC, ≥3000 cells/μL; platelets, ≥ 200,000/μL), serum bilirubin ≤1.5 mg/dL, serum creatinine ≤1.5 mg/dL, blood urea nitrogen ≤30 mg/dL, creatinine clearance >60 ml/min/1.73 m², and no prior cytotoxic chemotherapy. All patients underwent a complete history and physical examination. Laboratory evaluation included an automated blood and platelet count, 12-channel screening profile (alkaline phosphatase, lactate dehydrogenase, aspartate transglutaminase, blood urea nitrogen, creatinine, calcium, phosphorus, uric acid, total protein, albumin, and total bilirubin), serum acid phosphatase, prostate-specific antigen, and 24-h creatinine clearance. Written informed consent was obtained prior to initiation of therapy.

Patients initially received a 200-mg test dose of suramin over 15 min and, if no adverse reaction was observed, were started on a continuous infusion schedule regimen of 350 mg/m²/day. Because of the known adrenal toxicities associated with suramin, all patients received hydrocortisone, 25 mg orally every morning and 15 mg orally every evening, from the start of therapy. As per protocol, patients underwent weekly adjustments of suramin dose, based on the nomogram developed at the National Cancer Institute (10). To develop a population model, plasma suramin concentrations were monitored daily during the loading phase. The once-a-day sampling was chosen in view of the previously published half-life value for suramin (11, 15). The date and time of the sample, time from the previous determination, and the dose rate during the interval were recorded. If the dose rate changed during an interval between samples, the number of hours at each rate were considered as separate dose events. Following the discontinuation of the constant infusion, plasma suramin concentrations were determined every 7–14 days. Plasma suramin concentrations were assayed using the method of Kleecker and Collins (16), with a coefficient of variation of the assay for a given concentration of approximately 6%.

Data sets from seven patients, with a median of 29 plasma suramin determinations per patient (range, 9–37; total, 166), were utilized. All patients were receiving suramin for the first time. Individual data sets were initially analyzed with a maximum likelihood algorithm as applied by the computer program ADAPT II (17). The data was fit by a two-compartment open model (parameterized as two volumes, a distributional clearance and total body clearance; Fig. 1). The maximum likelihood algorithm also approximated error variance. The SD of an observation was assigned to be a linear function of suramin concentration, with variance described by the equation:

\[ \text{Variance} = k_1 \cdot (\text{suramin}_{\text{concentration}}) + k_2 \]  

where \( k_1 \) and \( k_2 \) are constants. The means of individual parameter estimates and the SD values of those means make up the population typical and population variable parameters for a S2S approach describing the population pharmacokinetic model for suramin (14, 18, 19). The S2S results were then used as an initial population model for subsequent analysis using an It2S method. The It2S approach to population modeling was implemented using a computer program developed and validated at the University of Maryland Cancer Center, Baltimore, MD (20). Fig. 2 shows the It2S algorithm. The population model estimated by the It2S approach was then used (a) as priors for the MAP-Bayesian estimator employed in subsequent analyses and (b) to generate the simulations described below.

To assess the validity of the population pharmacokinetic model and the feasibility of predicting subsequent plasma suramin concentrations based on a limited number of samples analyzed with the Bayesian algorithm included in ADAPT II, the following retrospective analysis was performed in each of the seven patients. Suramin concentrations measured at 24 and 48 h, along with the dosing history for that interval, were utilized to predict a plasma suramin concentration at 72 h. This prediction was then compared with the value actually measured at 72 h. The measured values at 24, 48, and 72 h were then used to predict the 96-h concentration. This procedure was repeated for all measured data points, both during and after the infusion. The MD from measured concentrations and the mean MAD of the predicted from the measured concentrations were then calculated as indicators of bias and precision, respectively. Bias refers to the tendency to err systematically in a positive or negative direction, and precision refers to quantification of the absolute magnitude of the error. These analyses indicated the ability to predict the plasma concentration profiles using sparse data (19).

Using the derived population pharmacokinetic model, we performed simulations for a proposed phase I trial to assess the suramin concentration profiles that might be anticipated. This simulated trial was designed to demonstrate the variability within the population using nonguided dosing. These simulated data sets were based on a 200-mg test dose followed by a loading dose of 810 mg/m² during 4 h. A fixed rate continuous infusion of 378 mg/m²/day would then be started after the loading dose and continued for 7 days. Plasma suramin concentrations were determined at the end of the loading dose on days 1, 2, and 3 (21). Simulations were performed using the SIM module of ADAPT II. In practice, individual pharmacokinetic parameters derived on day 3 will be used to estimate a continuous infusion dose rate for days 3 through 7 to produce a desired plasma suramin concentration on day 7. Twenty data sets were simulated, ignoring model variance, and an additional 20 data sets were simulated with “noise” using the variance model derived from the S2S analysis. The introduction of noise allows an assessment of the effects of unpredictable variations in measured parameters that might influence the measured results. These unpredictable variations include known factors, such as assay variability, and as yet uncharacterized patient factors, such as serum albumin or creatinine clearance, which might cause parameters to change with time (18, 20).

An LSS for the proposed phase I study was also developed. Individual parameter estimates from the final iteration of the It2S analysis were used, and the LSS was developed using Optimal sampling theory as applied by the SAMPLE module of ADAPT II. All analyses and simulations were performed on a Hewlett-Packard HP 9000/835 minicomputer running under the UNIX operating system.

RESULTS

Clinical Study. Patient characteristics are listed in Table 1. The plasma suramin concentrations observed during the first cycle in patients treated at 350 mg/m²/day by continuous infusion are listed in Table 2. The mean peak concentration achieved was 297 μg/ml (median, 297; range, 260–312 μg/ml). Two of the seven patients had plasma suramin concentrations (297 and 303 μg/ml) on days 9 and 10 which were prior to the “scheduled” day 14 sampling. Because of the development of septicemia, therapy was discontinued in one patient when the plasma suramin concentration was 260 μg/ml. The mean time to reach peak plasma suramin concentrations was 13.8 ± 5.2
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### Table 1 Patient demographics

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean ± SD</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>65.7 ± 7.9</td>
<td>52–75</td>
</tr>
<tr>
<td>Karnofsky performance status (%)</td>
<td>80</td>
<td>60–90</td>
</tr>
<tr>
<td>Body surface area (mg/m²)</td>
<td>2.02 ± 0.2</td>
<td>1.71–2.22</td>
</tr>
<tr>
<td>Creatinine (mg/dl)</td>
<td>0.98 ± 0.13</td>
<td>0.8–1.2</td>
</tr>
<tr>
<td>Albumin (g/liter)</td>
<td>4.27 ± 0.66</td>
<td>3.07–5.2</td>
</tr>
<tr>
<td>Alkaline phosphatase (units/liter)</td>
<td>50 ± 58</td>
<td>51–271</td>
</tr>
<tr>
<td>Acid phosphatase (units/liter)</td>
<td>16.5 ± 14</td>
<td>0.70–60.8</td>
</tr>
<tr>
<td>Prostate-specific antigen (ng/dl)</td>
<td>52 ± 53</td>
<td>0.7–271</td>
</tr>
</tbody>
</table>

### Table 2 Infusion characteristics

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean ± SD</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak level (µg/ml)</td>
<td>288 ± 20.9</td>
<td>260–312</td>
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<tr>
<td>Time to peak (days)</td>
<td>13.8 ± 5.2</td>
<td>7.7–21</td>
</tr>
<tr>
<td>Cumulative dose (g)</td>
<td>4.3 ± 0.9</td>
<td>3.0–5.6</td>
</tr>
<tr>
<td>Time (days) from peak to</td>
<td></td>
<td></td>
</tr>
<tr>
<td>150 µg/ml</td>
<td>11 ± 5.6</td>
<td>3–22</td>
</tr>
<tr>
<td>100 µg/ml</td>
<td>26 ± 11.4</td>
<td>13–43</td>
</tr>
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</table>

### Table 3 Pharmacokinetic parameters using the maximum likelihood algorithm

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean ± SD</th>
<th>% coefficient of variance</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>( V_1 ) (liters/m²)</td>
<td>4.53 ± 0.67</td>
<td>15</td>
<td>3.7–5.3</td>
</tr>
<tr>
<td>( V_2 ) (liters/m²)</td>
<td>10.32 ± 1.42</td>
<td>14</td>
<td>8.0–12.4</td>
</tr>
<tr>
<td>( CLd ) (liters/h/m²)</td>
<td>0.081 ± 0.024</td>
<td>29</td>
<td>0.051–0.12</td>
</tr>
<tr>
<td>( CLt ) (liters/h/m²)</td>
<td>0.017 ± 0.004</td>
<td>26</td>
<td>0.012–0.024</td>
</tr>
<tr>
<td>( t_{0α} ) (h)</td>
<td>25.2 ± 5.4</td>
<td>16.0–31.8</td>
<td></td>
</tr>
<tr>
<td>( t_{0β} ) (days)</td>
<td>29.7 ± 6.9</td>
<td>22.8–41.7</td>
<td></td>
</tr>
</tbody>
</table>

### Table 4 Analysis of It2S parameters and interpatient % coefficient of variance

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean</th>
<th>SD</th>
<th>% coefficient of variance</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>( V_1 ) (liters/m²)</td>
<td>4.38</td>
<td>20</td>
<td>2.9–5.2</td>
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</tr>
<tr>
<td>( V_2 ) (liters/m²)</td>
<td>10.3</td>
<td>4</td>
<td>10.0–11.1</td>
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<tr>
<td>( CLd ) (liters/h/m²)</td>
<td>0.083</td>
<td>45</td>
<td>0.069–0.094</td>
<td></td>
</tr>
<tr>
<td>( CLt ) (liters/h/m²)</td>
<td>0.017</td>
<td>23</td>
<td>0.013–0.024</td>
<td></td>
</tr>
<tr>
<td>( t_{0α} ) (h)</td>
<td>22.3</td>
<td>2.7</td>
<td>18.0–26.3</td>
<td></td>
</tr>
<tr>
<td>( t_{0β} ) (days)</td>
<td>28.2</td>
<td>5.0</td>
<td>22.4–35.5</td>
<td></td>
</tr>
</tbody>
</table>

Correlation matrix

\[ \begin{array}{ccc}
V_1 & V_2 & CLd \\
V_1 & 1 & 0.327 \\
V_2 & 0.407 & -0.256 \\
CLd & -0.094 & 0.831 \\
CLt & 0.677 & -0.379 \\
\end{array} \]

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Pharmacokinetic Modeling. A two-compartment open model was fit to each of the seven pharmacokinetic data sets. The means and SD values of the individual parameter estimates described using a maximum likelihood algorithm are listed in Table 3. The \( t_{0α} \) was 25.2 ± 5.4 h and the \( t_{0β} \) was 29.7 ± 6.9 days.

These parameter estimates were then used as the initial population pharmacokinetic model for the It2S analysis. Mean values for the constants, \( k_1 = 0.103 \) and \( k_2 = 1.35 \) estimated by the maximum likelihood algorithm, were used to describe the error variance in the subsequent It2S analysis. Error variance was assumed to be described by equation A.

Individual estimates of the half-lives for the \( α \) and \( β \) phases of suramin clearance were calculated from the individual parameter estimates derived from the It2S analysis in Table 4. The \( t_{0α} \) was calculated to be 22.3 ± 2.7 h (range, 18–26.3 h) and calculated \( t_{0β} \) was 28.2 ± 5 days (range, 22–35 days). The steady state volume of distribution \( V_{ss} \) of suramin \( (V_{ss} = V_c + V_p) \) was calculated to be 14.7 ± 1.1 liters/m². Intersubject variability in all parameters was generally small within this group of seven patients (23 ± 17%). In particular, intersubject variability in the volume of the peripheral compartment was very small (4%). This may reflect the similarities in age, sex, and disease status of the patients studied.

Validation of the LS/MAP-B Estimator Approach. The use of a limited number of plasma samples and a Bayesian algorithm for predicting plasma suramin concentrations was found to be unbiased (MD, 1.9 ± 14.5%) and precise (MAD, 11.1 ± 13%) when compared with measured plasma suramin concentrations. Fig. 3 shows a comparison between measured and LS/MAP-B fit estimates for plasma suramin concentrations in all seven patients. A clear linear relationship is apparent (\( r = 0.881 \), and...
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the regression line is similar to the line of identity. The measured values, full data fit, and LS/MAP-B estimates for patient I.T. are shown in Fig. 4. This demonstrates the suitability of the LS/MAP-B approach in this individual. Six of the seven data sets were well fit by the LS/MAP-B approach. However, one data set (M.F.) was poorly predicted using the LS/MAP-B approach (MD, 9.7 ± 17%; MAD, 20.2 ± 12.9%). However, the ADAPT II fit of the full data set for this patient was also imprecise. The reasons for this are unclear.

Simulation of the Proposed Regimen. The SIM program of ADAPT II was used in conjunction with the It2S derived population model to simulate 20 data sets that would be likely to be encountered in the proposed phase I protocol. Initially, error variance (noise) was not incorporated. Six representative simulated data sets are shown in Fig. 5. Data sets were selected because they contained the maximum or minimum predicted suramin concentrations at 168 h (7 days) or 936 h (39 days), respectively, and two further sets were selected because they depicted median values occurring at 168 or 936 h. These simulations demonstrate the range of plasma suramin concentrations (230—333 µg/ml at 168 h or 7 days and 47—143 µg/ml at 936 h or 39 days) predicted to occur in the proposed phase I trial if infusion rates were not individualized. In addition Fig. 6 show the 20 simulated data sets with noise, following the inclusion of error variance. The introduction of model variance shows that a measured peak suramin concentrations of 350 µg/ml can be anticipated in approximately 5% of patients at both 5 and 168 h.

Fig. 4. Precision of limited sampling strategy. Graph illustrating measured plasma concentrations in (µg/ml) and LS/MAP fit estimates. Data represent 151 samples from seven patients. ——, line of identity; ————, regression line. The correlation coefficient (r sq. 0.881) shows the precision of the fit.

Fig. 5. Data sets simulated without noise for proposed phase I trial. A, six individual simulations of the first 8 days during which patients receive a loading dose on day 1 and adjusted infusion rates on day 3 based on pharmacokinetic parameters calculated using the LS/MAP model. B, entire course during a 45-day period showing the variations in levels that would be observed after discontinuation of the infusion.

Fig. 6. Data sets simulated with model variance for proposed phase I trial. A, 20 simulations of the first 8 days during which patients receive a loading dose on day 1 and adjusted infusion rates on day 3 based on pharmacokinetic parameters calculated using the LS/MAP model. B, entire course during 45 days showing variations in the decay of plasma suramin concentrations.
LSS for Proposed Phase I Schedule. Optimal sampling theory as applied by the SAMPLE module of ADAPT II was used to define the most informative time points for sampling so as to allow assessment of the pharmacokinetics for an individual patient at 48 h (day 3). An initial pharmacokinetic estimation can be performed using the Bayesian algorithm, individual dosing history, and plasma suramin concentrations obtained at known, but not necessarily fixed, time intervals. Dose rates can then be adjusted to target the desired plasma concentration of 270 μg/ml ± 10% at 168 h (7 days) using the individual parameter values derived from the I12S analysis. A sampling strategy was defined for each of the seven patients using the individual parameter values derived from the I12S analysis. D-optimality was used as the criterion of a limited sampling strategy (19). The two most informative times for sample collections were immediately after the loading infusion and at 42 h (day 3). Thus, the planned time for adjustment of the infusion rate was 48 h. In addition, when a four-point sampling strategy was evaluated, these two times were duplicated, thereby emphasizing their importance. Therefore, in the proposed phase I study, sampling for pharmacokinetic estimation and dosing recommendations is planned for 30 min after the loading dose and at 42 h (21). In practice, a 6-h time period is allowed for assay determination, pharmacokinetic estimations, and dose rate adjustment.

DISCUSSION

Clinical use of suramin is complicated by a narrow therapeutic window. In reported trials, no responses were observed if peak plasma concentrations did not reach a minimum of 200 μg/ml, while the incidence of dose-limiting toxicities increased significantly at plasma concentrations >300 μg/ml (4). In one series, the incidence of neurotoxicity, which in its most severe form can progress to a Guillain-Barre syndrome requiring respiratory support, exceeded 40% when peak plasma concentrations >350 μg/ml were documented (5). Data from in vitro studies suggest that optimal administration of suramin may also require adequate exposure to therapeutic concentrations for prolonged time periods. In several systems, increasing the duration of exposure to a fixed concentration produced cytotoxic as opposed to cytostatic effects in vitro (15, 22–24). The observation of enhanced cellular proliferation at lower suramin concentrations further emphasizes the potential importance of a lower limit to the "window" (22). Therefore, allowing plasma suramin concentrations to decline before cell kill has occurred may adversely affect outcome.

Considering the plasma suramin concentrations in the seven patients treated in this study with a continuous infusion schedule, we found that the time to achieve the target concentration of 280–300 μg/ml ranged from 8–21 days. Two patients reached the target concentration at 9 and 10 days, which was prior to the scheduled weekly dose adjustment. Thus, when using a continuous infusion schedule, a minimum of biweekly plasma sampling is required. Of equal concern was that potentially subtherapeutic (<200 μg/ml) and potentially tumor-stimulating concentrations were observed as early as 3 days after discontinuation of the infusion.

In pharmacokinetic studies, a two-compartment open model adequately fit the available data. The modal parameter values for the volume of the central and peripheral compartments suggest limited distribution outside the extracellular fluid. This may reflect the extensive protein binding of suramin (14). The hypothesis that suramin plasma concentrations maintained within a therapeutic window correlates with response, and the analysis of the distributional and total body clearance of the drug, suggests a strategy for suramin dosing. During the first 1–3 weeks of treatment, suramin doses should be significantly dependent on distributional clearance, and when steady state concentrations have been achieved, suramin doses should be more dependent on total body clearance.

The lack of therapeutic efficacy observed in the present population may reflect inadequate exposure during the initial distributional phase of suramin treatment. Our proposed schedule modifications permit rapid saturation of the peripheral compartment and maintenance of adequate concentrations. A preliminary analysis in patients with prostatic and renal cell carcinoma has suggested a correlation of response with drug exposure as measured by area under the concentration time curve (25). The model simulations also support the need for individualized dosing. As shown in Fig. 5, variations from 120–250 μg/ml on day 2 and from 200–350 μg/ml on day 7 can be anticipated when using a schedule in which a bolus dose is followed by a continuous infusion at a fixed dose rate. The adaptive control algorithm described in this study can allow safe administration of suramin by permitting individualized dosing recommendations based on individual pharmacokinetic parameters.

The pharmacokinetic parameters of distributional (α) and elimination (β) half-lives observed in the current patient population were shorter than those previously reported (11, 12). This may reflect differences in the patient population, because earlier reports were based on patients with AIDS, who are generally younger, or differences in the duration of therapy. In addition, the AIDS patients reported were treated for an average of 20 weeks as compared to 2 weeks (range, 1–3 weeks) in the present study. Similar results were obtained for the AIDS patients when the data were fit to a one- or two-compartment model (11, 12); thus, it is unlikely that model differences explain the outcome. The presence of a third compartment, however, cannot be excluded.

Changes in renal function can also contribute to the observed differences. Suramin is not metabolized and renal excretion is the only route of elimination (17). Over time, patients treated with suramin do develop an increase in serum creatinine with a concomitant decrease in creatinine clearance. This may delay the overall clearance of the compound and effectively prolong the measured terminal half-life. In the present study, no significant changes in renal function were observed during the mean 14-day treatment period. In addition, the patients treated were relatively homogeneous with respect to baseline renal function, and the model considered only the first cycle of therapy. It is likely, however, that subsequent models, particularly those that explore longer durations of therapy, will need to consider changes in renal function, as well as changes in serum albumin, in the derivation. Because we are sampling at optimal times, as more data become available, the validity of the present model can be tested.

The use of the Bayesian methodology relies on measured population pharmacokinetic parameters for the initial treatment recommendations. As more concentrations on an individual patient become available, the derived values will approximate more closely the estimates obtained using the maximum likelihood algorithm. In the present study, the pharmacokinetic parameters estimated from the maximum likelihood method and summarized in a standard two-stage analysis were similar.
to those derived using the iterative two-stage analysis. This is best explained by the daily sampling strategy used and the median of 29 samples/patient from which the data were derived. The similarity of the mean absolute percentage difference of predicted from measured values (Fig. 3) and the error variance (10.3%) suggests that the imprecision contributed by the limited sampling maximum a priori Bayesian approach may be negligible. The small intersubject variability in the volume of the peripheral compartment may reflect the similarities in age, sex, and disease status within the patients studied. As more patients are evaluated, particularly those with other malignancies, the degree of variability will be better defined and the influence of other patient factors such as renal function and serum albumin can also be considered.

The advantage of the LS/MAP-B approach is that it permits estimation of the parameters of a patient early in the course of treatment and allows dose modifications based on the predictions of future plasma concentrations. This can limit the variability in plasma concentrations that would occur with a fixed rate schedule. While the iterative two-stage approach is currently only implementable on a minicomputer, once the maximum a priori Bayesian estimator has been derived, individual pharmacokinetic parameters can be estimated on a personal computer. Furthermore, the recent development of a rapid and facile high performance liquid chromatography assay method for suramin enhances the ability to calculate dosing recommendations on a timely basis (26).

The optimal sampling times were found to be at the end of the 4-h infusion and at 48 h. By obtaining plasma concentrations at these times, and modifying the infusion rate, the chance of exposure to subtherapeutic levels of suramin is reduced and additional drug can be administered. Furthermore, the chance of unexpectedly attaining plasma concentrations associated with toxic side effects is also reduced. The effects of a short exposure to high concentrations (>300 µg/ml) of suramin, however, remains unknown.

The population pharmacokinetic model describes herein can also be utilized for treatment using intermittent short infusions of suramin. The individual's calculated Vf can be used to determine the bolus dose required to return plasma suramin concentrations to the upper limit of the desired therapeutic range. This type of dosing schedule is currently under investigation in phase I trials of suramin at the University of Maryland (27, 28) and Memorial Sloan-Kettering Cancer Center where plasma concentrations are maintained in a specific range after the initial loading period (21). Use of the population pharmacokinetic model also allows prediction when a particular suramin concentration will be reached and, therefore, when repeat dosing is required.

In conclusion, based on our estimates of suramin pharmacokinetic parameters, new dosing strategies that allow maintenance of plasma concentrations in the proposed therapeutic window of 200–300 µg/ml are under study. A dosage regimen that quickly achieves a concentration in this range and maintains that level for a long period of time may improve outcome (28). Maintaining plasma concentrations in a desired range is feasible using the modified LS/MAP-B approach in conjunction with an assay that allows rapid turnaround of samples. The ability to control plasma concentrations will also be important as combination programs are developed (29).

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REFERENCES


Use of Adaptive Control with Feedback to Individualize Suramin Dosing


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