Suramin as a Chemosensitizer: Oral Pharmacokinetics in Rats

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Purpose. The purpose of this study was to determine if the 10–50 μM plasma concentrations of suramin required to produce chemosensitization could be achieved by oral administration.

Methods. Rats were given an oral dose of 100, 300, or 500 mg/kg unlabeled suramin by oral gavage. Rats receiving the 300 mg/kg oral dose of suramin also received a concomitant intravenous bolus injection of 50 μCi/kg of [^{3}H]suramin, administered 57 min after the oral dose. The intravenous data were used to calculate the clearance. Serial plasma samples were collected over 24–336 h. Plasma concentration-time profiles were analyzed using noncompartmental and compartmental methods. The pharmacokinetic parameters derived for the 300 mg/kg oral and 50 μCi/kg intravenous doses were used to calculate the bioavailability and AUC at the three oral dose levels.

Results. Plasma concentrations declined biexponentially following intravenous administration, with a distribution half-life of ~2 h and an estimated terminal half-life of 276 h. Suramin absorption following oral gavage was variable and incomplete with mean maximal plasma concentrations of 9.04, 72.6, and 64.4 μg/ml at doses of 100, 300, and 500 mg/kg, respectively. Seven of 15 rats exhibited two peak plasma concentrations at ~1 h and 3 to 12 h, suggesting the existence of multiple absorption sites and/or enterohepatic circulation. Oral bioavailability, calculated using the clearance of the intravenous tracer dose, was <3% at all three dose levels.

Conclusions. While plasma concentrations resulting from the 300 and 500 mg/kg oral doses of suramin were in the concentration range required to produce chemosensitization, the low bioavailability limits the usefulness of oral administration.

KEY WORDS: chemosensitizer; oral pharmacokinetics; suramin.

INTRODUCTION

Our laboratory recently reported an epigenetic, broad-spectrum mechanism of anticancer drug resistance caused by two fibroblast growth factors (FGFs) (i.e., acidic and basic FGF) that are expressed in solid tumors. These FGFs at clinically relevant concentrations induce up to 10-fold resistance to a wide array of chemotherapeutic agents with diverse structures and mechanisms of action (1). We further discovered that a nonspecific inhibitor of FGFs, suramin, completely reversed the FGF-induced resistance and enhanced the efficacy of multiple chemotherapeutic agents in cultured tumor cells and in multiple types of human xenograft tumors *in vivo* (1–3). The suramin chemosensitization effect applied to chemotherapeutics in multiple drug classes, that is, antimicrotubules (paclitaxel), topoisomerase inhibitors (doxorubicin, irinotecan), antimetabolites (5-fluorouracil, gemcitabine), and DNA alkylators (mitomycin C), as well as multiple tumor types, including primary and metastatic prostate, breast, colon, pancreatic, renal, and bladder tumors (1–8). The broadness of the suramin chemosensitization effect is unique; these encouraging preclinical results have motivated several clinical phase I/II trials in lung, breast and renal cancer patients. The phase II results in advanced non–small cell lung cancer patients suggest therapeutic benefits by adding suramin to the combination of paclitaxel and carboplatin (9,10). Compared to the results in patients with comparable prognostic factors and receiving only paclitaxel and carboplatin (11), the addition of suramin prolonged the median time to disease progression by about 100% (from 3 to 6 months) and the median survival time by about 40% (from 8 to 11 months). These improvements are substantial and warrant the testing of suramin in randomized trials.

Chemosensitization represents a new use for suramin. Suramin was first discovered in the early 1900s as an antiparasitic agent. The emergence of the AIDS epidemic in the early 1980s led to a wide spread effort to screen for agents with activity against human immunodeficiency virus. It was during this search that suramin was discovered to be a reverse transcriptase inhibitor. Suramin was then tested in AIDS patients, but was abandoned because of its life-threatening toxicities. Nonetheless, these trials led to the discovery of its antitumor property. Subsequent studies showed that suramin inhibits multiple growth factors. This, in turn, sparked considerable interests and efforts in developing it as an antitumor agent, since the early 1980s (12). At least 33 trials have been published (e.g., Refs. 13–22). In all these trials, suramin was used as a cytotoxic agent, at therapeutic plasma concentrations of between 100 and 200 μM (143–286 μg/ml). Suramin has also been tested in breast cancer patients as an antiangiogenic therapy, again requiring the maintenance of concentrations above 140 μM (18). At these concentrations, suramin shows significant toxicities and only modest activity in patients. Furthermore, suramin-containing combination therapy did not show a benefit over monotherapy. This has led to recommendations, by multiple investigators, against its future use (16–22). In late 1999, the U.S. Food and Drug Administration disapproved the use of high-dose suramin.

The major difference between the previous clinical studies with suramin and our ongoing studies is the intended use of suramin and, accordingly, the selection of the dose/concentration. Inhibition of FGFs requires only 10–20 μM suramin, a concentration that has neither cytotoxicity in cultured tumor cells nor toxicity in animals or patients. Another important consideration is the concentration-dependent effect of suramin on cell cycle kinetics. Suramin at concentrations above 50 μM arrests cells in the G1 phase (23–25). A blockage in the G1 phase may prohibit cells from progressing to the later phases such as the S and M phases where other agents exert their action. An example is the combination of suramin and radiation; suramin at 50 μM concentration caused cell cycle arrest in the G1 phase which in turn resulted in antagonism with radiation which is most effective in the

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ABBREVIATIONS: AUC, area under the plasma concentration-time curve; CL, plasma clearance; F, bioavailability; FGFs, fibroblast growth factors; MRT, mean residence time.

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G2/M phase (25). In contrast, the 10-20 μM concentration that we use to reverse the FGF-induced resistance does not cause G1 arrest and, therefore, is not expected to negatively affect the activity of chemotherapeutic agents.

Suramin is a symmetrical polysulfonated naphthylamine derivative of urea with a molecular weight of 1429.2 g/mol. Figure 1 shows its structure. Suramin is highly charged at physiologic pH (six negatively charged sulfonate groups) (26). Several studies evaluated the intravenous pharmacokinetics of suramin in humans and rodents (27–31). Based on its physicochemical properties, suramin was assumed to show a low oral bioavailability (32), but no study has been conducted to evaluate its oral absorption characteristics. As other compounds with similar physicochemical properties (e.g., pentosan polysulfate) are orally effective, and because the oral route would facilitate the clinical use of suramin, evaluation of the oral pharmacokinetics of suramin is worthwhile. We determined, in rats, the oral bioavailability of suramin at 100 to 500 mg/kg doses. Some animals were given concomitantly an oral dose of unlabeled suramin and an intravenous tracer dose of [^{3}H]suramin, and the clearance of the intravenous dose was used to calculate the bioavailability of the oral dose.

MATERIALS AND METHODS

Chemicals and Reagents

Radiolabeled suramin ([^{3}H]suramin sodium; specific activity, 12.5 Ci/mmol) was purchased from Moravek Biochemicals (Brea, CA, USA). Unlabeled suramin and trypan blue were purchased from Sigma Chemical Co. (St. Louis, MO, USA), isoflurane USP (Abbott Laboratories, North Chicago, IL, USA) from The Ohio State University Hospitals Pharmacy, and Atomlight liquid scintillation cocktail from Packard Bioscience (Meriden, CT, USA). All other chemicals and reagents were purchased from Sigma or Fisher Scientific (Pittsburgh, PA, USA) and were of HPLC or reagent grade.

Animal and Drug Treatment Protocol

Animals were cared for and handled according to the protocols approved by the Institutional Laboratory Animal Care and Use Committee. Male Copenhagen rats were purchased from Charles River Breeding Laboratories, Inc. (Raleigh, NC, USA) and had access to food and water *ad libitum*. Pretreatment body weights were 242 ± 14 g (mean ± SD, n = 15). One day before the study, permanent catheters (PE-50 Intramedic Clay Adams Brand polyethylene tubing, Becton Dickinson, Sparks, MD, USA) were implanted in the right carotid arteries of rats under light isoflurane anesthesia. Catheters were also implanted in the right jugular veins of rats receiving intravenous doses. The catheters were pulled under the skin and externalized through an incision in the back of the neck. Rats were housed in metabolism cages. On the day of the study, an oral dose of 100, 300, or 500 mg/kg of unlabeled suramin was administered by oral gavage (25, 75, or 125 mg/ml, respectively, in 0.9% NaCl) between 8 and 10 a.m. Rats receiving the 300 mg/kg oral dose of suramin also received an intravenous bolus injection of 50 μCi/kg of [^{3}H]suramin (25 μCi/ml in 0.9% NaCl), administered 57 min after the oral dose. The delay was to allow for a potential lag time for the absorption of the oral dose so that the plasma concentrations derived from the oral dose would be at their maximal values. Serial blood samples were collected over 24–336 h, and immediately centrifuged. The blood sample volume removed from the rats was replaced with an equivalent volume of 0.9% NaCl containing 10–100 U/ml heparin. Plasma samples were stored frozen at –30°C until analysis. Blood samples (250 μl) were withdrawn from the carotid catheter during the first week of the study. As catheter patency became problematic after about one week, a terminal sample was collected at two weeks.

Sample Analysis

Plasma samples were analyzed as previously described (33) with minor modifications. Trypan blue was used as the internal standard, and UV absorbance at 313 nm was monitored (34). Plasma samples (100–125 μl) were mixed with trypan blue (10 μl of 200 μg/ml), 100–125 μl of 0.5 M tetrabutylammonium bromide (pH 8.0), and 200–250 μl of acetonitrile and stored at 4°C for >2 h. Following centrifugation at 14,000 × *g* for 10 min, 20–40 μl of the supernatant were injected into the HPLC system (Agilent Technologies 1100 Series HPLC, Palo Alto, CA, USA). The limit of suramin detection was ~1 μg/ml, or 7% of the lowest desired concentration (10 μM or 14.3 μg/ml). This limit of detection was also estimated to be high enough to determine a bioavailability of 2% at the lowest dose administered, and hence considered sufficiently sensitive for the study. For analysis of [^{3}H]suramin concentrations, 20 μl of plasma was mixed with 10 ml of Atomlight liquid scintillation cocktail, and total radioactivity was determined by liquid scintillation counting using a Packard Tri-Carb liquid scintillation analyzer (Meriden, CT, USA). The counting efficiency was ~50%. Plasma concentrations of [^{3}H]suramin were generally <1% of the total suramin concentrations. In some cases, plasma concentrations of [^{3}H]suramin were as high as 4% of the total suramin concentrations; these [^{3}H]suramin concentrations were subtracted from the total suramin concentrations measured by UV absorbance.

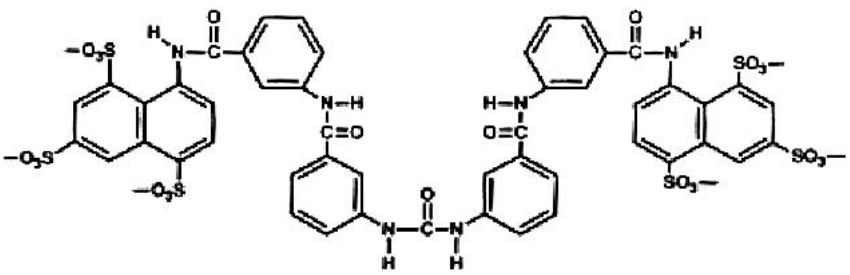

Fig. 1. Chemical structure of suramin.

Pharmacokinetic Data Analysis

Plasma concentration-time data of the 300 mg/kg oral doses and 50 μCi/kg intravenous doses were analyzed by WinNonlin v4.0 (Pharsight Corporation, Mountain View, CA, USA) using both noncompartmental and compartmental methods. In the noncompartmental analysis, the area under the plasma concentration-time curve (AUC) and the area under the first moment curve (AUMC) were calculated by the trapezoidal rule. The plasma clearance (CL) of suramin after intravenous administration was calculated as dose divided by AUC. The mean residence time (MRT) was calculated as AUMC divided by AUC, and the volume of distribution at steady state (Vd_{ss}) was calculated as the product of MRT and CL. In the compartmental analysis, two- and three-compartment models with elimination from the central compartment were fitted to plasma concentration-time profiles. Best-fit parameters were obtained using Gauss-Newton least-squares regression analysis, and the goodness of fit of the models to the experimental data was compared using the Akaike information criterion and Schwartz criterion (35). The bioavailability (F) of the oral unlabeled suramin was calculated as the product of (AUC of unlabeled suramin) and (clearance of [^{3}H]suramin) divided by (dose of unlabeled suramin).

Because the terminal phases of the plasma concentration-time profiles of the 100 and 500 mg/kg oral doses of suramin were not completely characterized, the elimination rate constant of the 300 mg/kg oral dose was used to calculate the AUC of the 100 and 500 mg/kg oral doses. Four rats in the 100 mg/kg dose group showed plasma concentrations below the detection limit of 2 μg/ml; the upper limits of the F values in these animals were calculated using the limit of detection as the concentration.

RESULTS

Pharmacokinetics of the Intravenous Dose

The plasma concentration-time profile of suramin following intravenous administration of a 50 μCi/kg dose is shown in Fig. 2, and the pharmacokinetic parameters are summarized in Table I. As suramin is not metabolized *in vivo* (28,36), the total radioactivity represented the parent drug. The intravenous data were equally well described by a two-compartment model and a three-compartment model, as indicated by similar Akaike Information Criterion (−91.6 vs −92.6) and Schwartz Criterion (−88.9 vs. −88.6) values. Hence, the simpler two-compartment model was used to analyze the data. Suramin was cleared slowly. Plasma concentrations declined biexponentially with a distribution half-life of about 2 h and a terminal half-life of 276 h. CL was 2.08 ± 0.28 ml h^{-1} kg^{-1}, which is <1% of the glomerular filtration rate (37). The initial volume of distribution of the central compartment of 57.1 ± 12.3 ml/kg was approximately equal to the plasma volume, whereas the volume of distribution at steady state was similar to the total body water volume of 670 ml/kg (37).

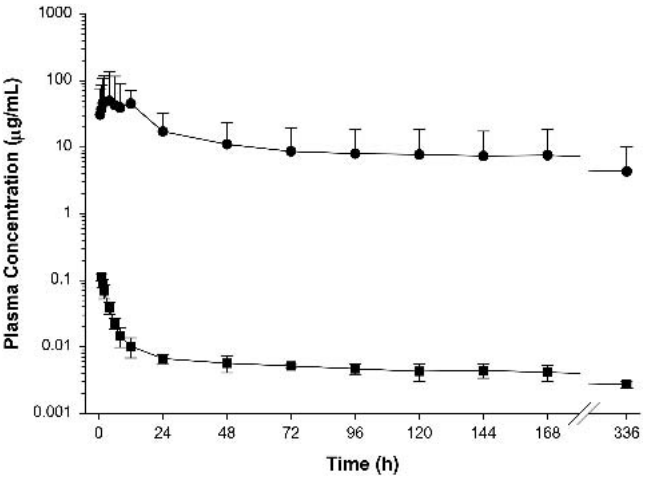

Fig. 2. Plasma concentration-time profiles of suramin following oral and intravenous administration in rats. Rats were given an oral dose of 300 mg/kg unlabeled suramin by oral gavage (closed circles) and, 57 min later, an intravenous dose of 50 μCi/kg of [^{3}H]suramin (closed squares). Mean ± SD, n = 5.

Pharmacokinetics of the Oral Dose

The oral absorption of suramin was highly variable and incomplete with mean maximal plasma concentrations of 9.04, 72.6, and 64.4 μg/mL at doses of 100, 300, and 500 mg/kg, respectively (Fig. 3; Table II). The unexpectedly high maximal plasma concentrations after 300 mg/kg, when compared to the results of the 500 mg/kg group, were due to a much higher drug absorption in a single rat receiving 300 mg/kg (Table II). Seven of 15 rats exhibited two peak plasma concentrations at ~1 h and between 3 to 12 h, suggesting the existence of multiple absorption sites in the gastrointestinal tract and/or enterohepatic circulation (38). Oral bioavailability, calculated using CL of the intravenous tracer dose, was <3%, on average, for all doses investigated. Only one rat showed a bioavailability of >2%. Suramin was not detectable in plasma in over 50% of the rats (4 of 7) that received the 100 mg/kg dose.

Table I. Pharmacokinetic Parameters of Suramin Following Intravenous Administration

Rat	$AUC_{0\to\infty}$ (h · μCi/ml)	CL (ml/h^{-1} kg^{-1})	MRT (h)	Vd_{ss} (ml/kg)	V_1 (ml/kg)	$t_{1/2,\alpha}$ (h)	$t_{1/2,\beta}$ (h)
1	25.1	1.99	620	1020	52.4	1.90	468
2	27.3	1.84	409	699	38.7	1.24	307
3	21.3	2.35	202	581	68.3	2.16	158
4	28.0	1.80	319	846	68.0	2.12	249
5	21.1	2.40	250	616	58.2	2.12	197
Mean	24.6	2.08	360	752	57.1	1.91	276
SD	3.2	0.28	165	181	12.3	0.39	121

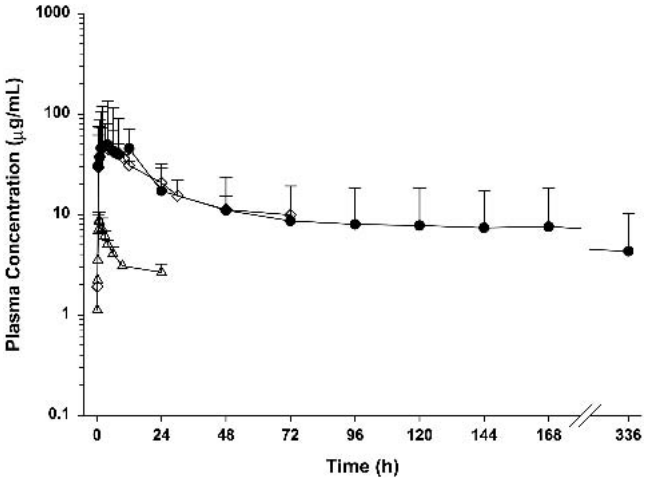

Fig. 3. Plasma concentration-time profiles of suramin following oral administration of different doses in rats. Rats were given an oral dose of 100, 300, or 500 mg/kg unlabeled suramin by oral gavage. One hundred mg/kg (open triangles, n = 3). Three hundred mg/kg (closed circles, n = 5); same as the group depicted in Fig. 2. Five hundred mg/kg (open diamonds, n = 3). Note the overlapping concentrations in the 300 and 500 mg/kg groups, due to variable drug absorption (see rat no. 2 in Table II). The 100 mg/kg oral suramin plot is composed of data from the three rats that showed detectable concentrations (i.e., rats 6–8 in Table II). The plasma concentrations of the unlabeled suramin were corrected for the [^{3}H]suramin concentrations, which contributed up to 4% of the total concentrations.

DISCUSSION

Results of this study show incomplete and highly variable absorption of suramin in rats, following oral administration. The bioavailability was <3%. Suramin is stable at body temperature and at the pH range observed in the gastrointestinal tract. About 2% of suramin is hydrolyzed after 42 days at 37°C (39). The half-life of suramin is ~16 h at the pH of the stomach contents of ~2 (40,41), and >18 h at the pH of the duodenum of 6–8 (41). Degradation of suramin is more rapid at extremely high or low pH, with a degradation half-life of <5 h at pH <1 or >12.5 (41). Based on a gastrointestinal transit time of ~1.5 h in rats and assuming the pH range of 2–8 throughout the gastrointestinal tract (37), we calculated that degradation would be negligible, accounting for ~5% of an oral dose. Accordingly, the low bioavailability was primarily due to lack of absorption. The low oral bioavailability of suramin is in agreement with Lipinski's "rule of 5," which predicts poor absorption for a drug that satisfies any two of the following four criteria: (a) a molecular weight of >500 g/mol, (b) a Log $P_{octanol:water}$ of >5, (c) more than 5 hydrogen bond donors (sum of OHs and NHs), and (d) more than 10 hydrogen bond acceptors (sum of Os and Ns) (42). Suramin satisfies three of the four criteria; the log P of suramin is –3.5 (43).

Suramin shows dose-dependent pharmacokinetics in human patients; the terminal half-life was 41 days after the high doses used to produce cytotoxicity (requiring plasma concentrations of 140–280 μg/ml) and was 5-fold shorter at 8.6 days after the low doses used to produce chemosensitization (re-

Table II. Pharmacokinetic Parameters of Suramin Following Oral Administration

Rat	$AUC_{0\rightarrow\infty}$ (h · μg/ml)	Overall C_{max} (μg/ml)	Overall t_{max} (h)	C_{max1} (μg/ml)	t_{max1} (h)	C_{max2} (μg/ml)	t_{max2} (h)	t½ (h)	F (%)
100 mg/kg									
6	729	9.63	1.0	9.63	1.0	NA	NA		1.5
7	799	10.7	0.75	10.7	0.75	NA	NA		1.7
8	886	6.83	0.75	6.83	0.75	5.23	3.0		1.8
9	<616	<2.0	ND	ND	ND	ND	ND		<1.3
10	<616	<2.0	ND	ND	ND	ND	ND		<1.3
11	<628	<2.0	ND	ND	ND	ND	ND		<1.3
12	<628	<2.0	ND	ND	ND	ND	ND		<1.3
Mean[a]	805[a]	9.04[a]	0.83[a]	9.04[a]	0.83[a]	5.23	3.0		<1.5
SD	78.5	1.98	0.14	1.98	0.14				0.2
300 mg/kg									
1	2782	43.6	1.5	43.6	1.5	40.0	8.0	249	1.8
2	14,350	203	4.0	203	4.0	NA	NA	229	8.7
3	806.4	31.2	12	2.20	1.0	31.2	12	172	0.73
4	1954	55.3	12	5.20	0.5	55.3	12	188	1.2
5	1485	30.0	1.5	30.0	1.5	19.3	12	170	1.2
Mean	4276	72.6	6.2	56.8	1.7	36.5	11	202	2.7
SD	5679	73.6	5.4	83.6	1.4	15.2	2.0	36	3.4
500 mg/kg									
13	2611	34.7	10	18.3	1.0	34.7	10		1.1
14	4604	79.5	1.0	79.5	1.0	50.3	6.0		1.9
15	4283	79.0	4.0	79.0	4.0	NA	NA		1.8
Mean	3833	64.4	5.0	58.9	2.0	42.5	8.0		1.6
SD or range	1070	25.7	4.6	35.2	1.7	34.7–50.3	6–10		0.4

The pharmacokinetic parameters derived for the 300 mg/kg oral and intravenous doses were used to calculate the F and AUC of the 100 and 500 mg/kg oral doses. NA, not assessed because only one C_{max} was detected. ND, below the limit of quantification of 1–2 μg/ml.
[a] Calculated using data for rats 6–8 only.

quiring plasma concentrations of 14–71 μg/ml) (44). By administering the intravenous dose during the disposition of the oral dose, we obtained an estimate of drug disposition at the concentrations resulting from oral administration, thereby reducing the effect of possible dose-dependent pharmacokinetics on bioavailability estimates.

The terminal half-life of [^{3}H]suramin of 276 h or 11.5 days observed in the current study is shorter compared to the value of ~39 days estimated from autoradiography analysis of [^{14}C]suramin disposition in an earlier study, also in rats (36). The suramin dose in the earlier study was 300 mg/kg. In comparison, the dose used in the current study was calculated to be about 10 mg/kg, that is, the sum of the intravenous [^{3}H]suramin tracer dose of about 1.5 mg and the maximal bioavailability of the oral dose of <2% of 500 mg/kg. Based on the observation in humans where the dose-dependent suramin kinetics resulted in a 5-fold longer half-life at a 10-fold higher dose, we propose that the 3.5-fold longer half-life in the [^{14}C]suramin study was due to dose-dependent pharmacokinetics. A second contributing factor could be the relatively short duration in the present study (i.e., 14 days) as opposed to 84 days in the earlier study. Extension of the study duration was experimentally complicated as the catheters were no longer patent, and was unlikely to alter the conclusion of low and variable bioavailability.

The goal of the current study was to determine if the 10–50 μM plasma concentrations of suramin required to produce chemosensitization could be achieved by oral administration. Although plasma concentrations resulting from 300 and 500 mg/kg oral doses of suramin were in this concentration range, the low bioavailability limits the usefulness of oral administration. An increase of the bioavailability to ~10%, as observed in one rat that received a 300 mg/kg oral dose, would result in plasma concentrations >50 μM which, as discussed in the "Introduction," would render suramin ineffective. Furthermore, the rate of suramin absorption was highly variable, as indicated by the wide range of times to reach peak plasma concentrations (1 to 12 h).

CONCLUSIONS

The results of this study indicate that oral administration of suramin is not an attractive means of delivery because only negligible amounts are absorbed into the systemic circulation following oral administration. Although plasma concentrations were in the range required for inhibition of FGFs, oral administration of suramin is not recommended due to variable and incomplete absorption.

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