Mineralocorticoid Insufficiency Due to Suramin Therapy

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BACKGROUND. During a Phase I trial of suramin, a novel antineoplastic agent with activity against hormone-refractory prostate carcinoma, the authors observed two patients with clinical mineralocorticoid insufficiency in spite of hydrocortisone replacement therapy.

METHODS. The authors retrospectively assessed adrenal cortical function in 20 such patients via adrenocorticotropic stimulation testing, measuring both cortisol and aldosterone responses, either at the time of treatment or immediately after discontinuation of treatment.

RESULTS. Two of 9 patients (22%) treated at relatively low dose levels ($\leq$1200 mg/m^2 on Day 1) demonstrated adrenal cortical insufficiency, as compared with 9 of 11 patients (82%) treated with relatively high doses (>1200 mg/m^2 on Day 1) (P = 0.03 by 1-tailed Fisher's exact test). There appeared to be a cumulative dose-response relationship to the development of glucocorticoid insufficiency, with no instances being observed at doses < 4.8 g/m^2 and uniform toxicity occurring at doses > 7.6 g/m^2. Long term glucocorticoid insufficiency was present in 1 of 5 patients (20%) tested at an interval of >90 days after discontinuation of suramin treatment. All instances of glucocorticoid insufficiency were associated with mineralocorticoid insufficiency. Suramin did not affect the absorption or excretion of exogenously administered glucocorticoid in one patient.

CONCLUSIONS. Suramin causes both primary mineralcorticoid and primary glucocorticoid insufficiency. This may occur in a dose-dependent manner. Long term glucocorticoid insufficiency appears to occur in a minority of patients treated with low doses of suramin. Patients receiving high doses of suramin for treatment of advanced carcinoma should receive at least physiologic replacement doses of both mineralocorticoid and glucocorticoid. Higher doses of glucocorticoid may be required in selected patients. ***Cancer* 1996; 78:2411–20.**

KEYWORDS: suramin, fludrocortisone, adrenal cortical insufficiency, glucocorticoid, mineralocorticoid, dose response, dose toxicity, hydrocortisone.

Primary adrenal insufficiency occurs as a result of treatment with several agents, including aminoglutethimide,[1] mitotane (o,p'-

Presented in part at the 76th Annual Meeting of The Endocrine Society, Anaheim, California, June 15–18, 1994.

Supported by Grant #2-T32-CA-09566-06 and Contract #N01-CM-07301 from the National Cancer Institute, Grant #5-T32-GM07019-18 from the National Institute of General Medical Sciences.

Dr. Vogelzang is supported in part by the Foster Schlutz Memorial Fund for Cancer Research and the Klein Family Fund.

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Dr. Weiss is supported by Grant #DK02081 from the National Institutes of Health and by Morris and Cynthia Belzberg.

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Received March 15, 1996; revision received July 1, 1996; accepted July 5, 1996.

DDD),[2] itraconazole,[3] ketoconazole,[4] metyrapone,[5] etomidate,[6] rifampin,[7–10] treosulfan,[11] heparin,[12–16] trilostane,[17] and suramin.[18] These drugs in general exert their adrenocortical effects by inhibiting the activity of various enzymes involved in glucocorticoid and mineralocorticoid biosynthesis, such as 11β- and 18β-hydroxylase, cholesterol side-chain cleavage enzyme, and 17,20-lyase. Suramin, a new antineoplastic agent, appears to interfere with the binding and effects of autocrine growth factors, and has attracted much attention by virtue of its activity in treating hormone-refractory metastatic prostate carcinoma. Suramin causes adrenal cortical necrosis and adrenal insufficiency in some patients and as a result, all trials to date have routinely employed replacement doses of hydrocortisone. However, mineralocorticoid supplementation is not routinely prescribed. While conducting a Phase I study of suramin, the authors observed two instances of addisonian crisis occurring despite presumably adequate replacement doses of hydrocortisone. Both patients underwent adrenocorticotropic hormone (ACTH) stimulation testing and were found to have severe mineralocorticoid insufficiency. Therefore a retrospective analysis was undertaken of adrenal function in surviving patients from whom verbal informed consent was obtained. In this report, those findings are described and guidelines for glucocorticoid and mineralocorticoid replacement in patients receiving suramin are suggested.

PATIENTS AND METHODS

The protocol for suramin (described elsewhere[19]) required that all patients receive hydrocortisone, 25 mg orally every morning and 10 mg orally every evening while receiving suramin by intermittent infusion. Patients remained on this dose of hydrocortisone for the duration of suramin treatment and, except for the two cases noted, continued on this dose until the time of endocrine testing or death. Informed consent was obtained from all patients prior to entry into the protocol and prior to adrenal function testing. In view of suramin's extremely long half-life of 30–50 days, the dosing scheme, unlike previous studies, gradually used decreasing doses to maintain constancy of the peak plasma levels. These decreases were made in accordance with a prespecified scheme, rather than measured plasma levels. A standard Phase I dose escalation design was employed, in which patients were enrolled successively in cohorts receiving gradually increasing doses of suramin until a maximally tolerated dose was attained. Each dose level was expanded as necessary to more precisely characterize the toxicity profile of this drug as given in this dosing schedule. Eight dose levels (400, 600, 800, 1000, 1200, 1440, 1730, and 2080 mg/m^2 on Day 1) were explored. The initial cohort, at a dose of 400 mg/m^2 on Day 1, received a total of 960 mg/m^2 of suramin over the 1st month; the final cohort, at a dose of 2080 mg/m^2 on Day 1, received a total dose of 4992 mg/m^2 over the first month. Sixty-three patients were treated according to a schedule in which progressively decreasing doses of suramin were administered on Days 1, 2, 8, and 9 of each 28–day cycle. This regimen was designed to avoid gradually increasing peak plasma levels over the treatment course. An additional 13 patients were treated using a modification of the original schedule (schedule A), in which the 2 doses in each week were consolidated into 1 dose (i.e., Days 1 and 2 were administered on Day 1, and Days 8 and 9 were administered on Day 8). Although this modification simplified the logistic aspects of the dosing scheme, the total monthly amount of suramin was identical in both schedules. Written informed consent was obtained from all patients, in accordance with federal and institutional guidelines.

Because the majority of patients enrolled in the Phase I study were men with hormone-refractory metastatic prostate carcinoma, the baseline evaluations required by the protocol did not routinely include abdominal computed tomography (CT) scanning. However, CT scans were performed as clinically indicated for those prostate carcinoma patients with known extraosseous disease and routinely for those patients with malignancies other than prostate carcinoma.

Endocrinologic evaluations were not mandated by the protocol; however, posttreatment ACTH stimulation testing was discussed with patients as they discontinued treatment to assess their need for ongoing glucocorticoid replacement. At the time this study was initiated, all surviving patients who had discontinued suramin treatment were contacted and asked to undergo ACTH testing. Twenty of the 76 patients originally enrolled agreed to undergo testing with the rapid ACTH test, assessing both cortisol and aldosterone response.[20] The remaining 56 patients were either lost to follow-up, had died prior to being contacted, or refused endocrine testing. All 20 patients were ambulatory outpatients who were able to present themselves to either their local medical center or to the University of Chicago Hospitals for testing.

Patients withheld their doses of hydrocortisone for 24 hours prior to ACTH stimulation testing. After obtaining baseline ACTH, aldosterone, and cortisol levels, 0.25 mg of cosyntropin was injected intravenously. Cortisol and aldosterone levels were measured at 30 and 60 minutes after injection. ACTH, cortisol, and aldosterone levels were measured in the hospital clinical laboratories using commercially available radioimmunoassay kits (ACTH: Nichols Institute Diagnostics,

San Juan Capistrano, CA; cortisol and aldosterone: Coat-A-Count, Diagnostic Products Corporation, Los Angeles, CA). The assay limits of sensitivity were 16 pg/mL for aldosterone and 0.2 μg/dL for cortisol. A test was considered abnormal if the serum cortisol at 60 minutes after administration of ACTH failed to rise by >7 μg/dL over the baseline and if it failed to reach a level of 18 μg/dL.[21] Aldosterone stimulation testing was considered to be abnormal if the baseline level was below 5 ng/mL and if the level at 60 minutes failed to rise by 5 ng/mL over the baseline value.[20] The results of ACTH stimulation testing using a similar protocol in 19 normal volunteers were kindly furnished by Nichols Institute Diagnostics (Jerrold Nelson, personal communication). ACTH, cortisol, and aldosterone concentrations in these volunteers were measured using the same methods as already described.

Suramin plasma concentrations were determined using a high-performance liquid chromatography assay method as previously described.[19]

The design of the bioavailability study called for the oral administration of 20 mg of hydrocortisone on Day 1, followed by hourly collection of plasma samples over the next 8 hours. On Day 2, 20 mg of hydrocortisone was administered intravenously and hourly sampling was again obtained. Cortisol concentrations were determined using the same assay as described above.

Examination of scatter plots relating absolute change and percentage change after ACTH stimulation to the baseline values of cortisol and aldosterone showed a strong dependence of the percentage change on baseline, whereas absolute change was relatively independent of the baseline. Accordingly, absolute change was used in the statistical analyses.[22] One-way analysis of variance with Bonferroni's correction for post hoc analyses, Spearman's rank order correlations (r), logistic regression analyses, nonparametric tests, chi-square, and Student's *t* tests were performed using SPSS for Windows, version 6.1.2.[23] Two-compartment linear models were fit to the bioavailability data using the nonlinear least-squares fitting program PCNONLIN, version 4.0 (Scientific Consultants, Inc., Lexington, KY). Systemic bioavailability, quantified as the ratio of the area under the concentration × time curve (AUC) after oral administration to the AUC after intravenous administration,[24] was calculated using the linear trapezoidal method with extrapolation to infinity.

RESULTS

ACTH Stimulation Testing

Table 1 shows selected characteristics of the two patient populations. The median age at the start of suramin therapy differed significantly ($P = 0.03$), as did the total received dose of suramin ($P = 0.03$), and the last recorded suramin concentration prior to ACTH stimulation testing ($P = 0.002$). This last result, however, should be interpreted with caution, because the plasma concentrations could not be determined at a uniform time relative to the time of ACTH testing. The time from the last dose of suramin to the time of ACTH stimulation testing was not significantly different between the two groups ($P = 0.06$).

The ACTH stimulation test results of the 20 patients are shown in Table 2. The occurrence of abnormal ACTH stimulation tests correlated with dose level (Spearman's r = 0.67; $P = 0.001$) (Table 2). This is most strikingly illustrated by the fact that only 2 of 9 (22%) patients treated below the 1200 mg/m^2 on Day 1 dose level who underwent ACTH stimulation testing after discontinuation of suramin had abnormal cortisol and aldosterone responses, whereas 9 of 11 (82%) patients treated at or above the 1200 mg/m^2 dose level had abnormal responses. All patients who demonstrated impaired glucocorticoid responses to ACTH stimulation also demonstrated impaired or absent mineralocorticoid responses, indicating defects in both mineralocorticoid and glucocorticoid function.

Table 3 compares the summary results of ACTH stimulation testing performed on 19 normal control subjects (J. Nelson, personal communication) with the results of the current study patients taken in their entirety. The extent of glucocorticoid responsiveness to ACTH stimulation, measured by the delta (Δ) cortisol, had a mean for the control subjects of 15 ± 4.2 μg/dL, as compared with 6.4 ± 6.8 μg/mL for all patients irrespective of dose level ($P < 0.001$). Considerable variability in suramin's pharmacologic effect on the adrenal gland was noted among the patients; the effect of dose accounted for a large part of this variability, because Δ cortisol correlated well with dose cohort (Spearman's r = −0.74; $P < 0.001$). When patients treated at doses from 400 mg/m^2 on Day 1 to 800 mg/m^2 on Day 1 were grouped together and compared against patients treated at higher dose levels and against control subjects (Table 3), statistically significant differences ($P = 0.05$) between patients and normal controls were found in the aldosterone responses to ACTH stimulation.

In comparing the cumulative received doses of those patients with and without abnormal responses to ACTH stimulation (Fig. 1), it appears that at doses below 9.6 g (4.8 g/m^2), the incidence of adrenal insufficiency is minimal, whereas at doses above 17 g (7.6 g/m^2) there is uniform occurrence of adrenal insufficiency. At intermediate doses, other factors besides drug effect may be important. Logistic regression analysis evaluating the effect of cumulative dose on the

TABLE 1
Patient Characteristics

Characteristic	Glucocorticoid			Mineralocorticoid		
	No	Yes	*P* value[a]	No	Yes	*P* value[a]
No. of patients	10	10		6	10	
Age (yrs)	69 (39–76)	60 (34–71)	0.03	67 (39–74)	60 (34–76)	0.55
Albumin, mg/dL	4.1 (3.7–4.6)	4.2 (3.8–4.7)	0.76	4.1 (3.7–4.6)	4.1 (3.8–4.7)	0.66
Creatinine, mg/dL	1.3 (1–1.6)	1.2 (1–2)	0.42	1.2 (1–1.4)	1.2 (1.1–2)	0.69
KPS, %	90 (80–100)	90 (80–100)	0.63	85 (80–100)	90 (80–100)	0.12
Hemoglobin, g/dL	11.7 (8.8–15.2)	13.3 (8.2–14.9)	0.21	11.6 (10.2–15.2)	13.3 (8.2–14.9)	0.87
No. of cycles	5.5 (1–16)	3 (2–4)	0.22	4.5 (1–16)	3.5 (1–10)	0.07
Total dose, mg	11,300 (3994–17,095)	15,586 (9648–21,908)	0.04	11,300 (8553–17,017)	16,615 (3994–21,908)	0.06
Total dose, mg/m^2	6072 (1920–9241)	8349 (4824–11,065)	0.03	6270 (4152–8157)	9134 (1920–11,064)	0.05
Last concentration, μg/dL	39.6 (4.5–129.9)	168.5 (46.4–237.4)	0.001	20.1 (4.5–117.7)	123.1 (36.1–237.4)	0.01
Time from last dose to endocrine testing, days	75 (30–610)	34 (9–145)	0.06	35 (30–231)	35 (9–362)	0.39

KPS: Karnofsky performance status.
[a] Mann-Whitney *U* test.

occurrence of an abnormal ACTH stimulation test confirmed the importance of total received dose, whether expressed as the raw total or as the total dose normalized to body surface area (Table 4). The odds of having an abnormal cortisol response to ACTH stimulation is increased 216% for each g/m^2 of administered suramin ($P < 0.005$). Although a significant proportion of the data on aldosterone response to ACTH stimulation were missing, similar analyses did not demonstrate a statistically significant effect of dose.

No association of tumor response either for all patients or for only the prostate carcinoma patients with impaired glucocorticoid or mineralocorticoid response could be found (Table 2). Baseline CT scans were available in seven patients (one with breast carcinoma, two with sarcoma, and four with prostate carcinoma), including the two patients mentioned above. The adrenal glands in five patients were normal. Abnormalities of the adrenal gland were noted in two patients, one of whom (Patient 416), demonstrated a normal cortisol ACTH stimulation test. Metastasis to the adrenal glands developed over the course of the study in one other patient (Patient 476), who demonstrated impaired glucocorticoid responsiveness to ACTH stimulation. Two patients required hospitalization and parenteral fluid and electrolyte support for addisonian crises and continued to have severe adrenal insufficiency despite the use of increasing doses of glucocorticoid. The need for such intensive measures largely abated after the institution of mineralocorticoid replacement with fludrocortisone.

Bioavailability of Hydrocortisone

A patient (Patient 456) with repeated episodes of addisonian crisis in spite of fludrocortisone and hydrocortisone replacement therapy underwent a bioavailability study to assess his ability to absorb orally administered hydrocortisone. As can be seen in Figure 2, after an oral dose of hydrocortisone (20 mg) and an intravenous dose of hydrocortisone (20 mg), the concentration time profile is identical, demonstrating an unimpaired ability to absorb hydrocortisone. Consistent with this, the systemic bioavailability of hydrocortisone was 100%. The elimination half-life of hydrocortisone was also normal.

DISCUSSION

The occurrence of adrenal glucocorticoid insufficiency during treatment with suramin has been described previously[18] and is well known. However, mineralocorticoid insufficiency has been hitherto unsuspected,

TABLE 2
Treatment and ACTH Stimulation Test Data in 20 Patients Treated with Suramin

Patients ID[a]	Tumor response[b]	Cohort (mg/m^2 on Day 1)	Total dose (mg/m^2)	Days from last dose to ACTH test	Concentration ($\mu g/mL$)	Days from concentration to ACTH test	ACTH[c] (pg/mL)	Cortisol 0 mins ($\mu g/dL$)	Cortisol 60 mins ($\mu g/dL$)	ΔCortisol[d] ($\mu g/dL$)	Aldo 0 mins (ng/dL)	Aldo 60 mins (ng/dL)	ΔAldo[d] (ng/dL)
407	Yes	600	6040	3	10	17	2	13.3	33	19.70	14.8	35.4	20.60
410	No	600	5902	36	4.5	22	9	13.7	30	16.30	10	30.7	20.70
415	Yes	800	8157	35	15.2	5	16	9.7	22	12.30	10.7	23.4	12.70
416[e]	No	800	1920	87	43.2	74	20	21.8	31.8	10.00	NA	NA	NA
470	Yes	800A	1920	362	59.9	317	NA	6.3	18.6	12.30	4.4	5.7	1.30[f]
423	Stable	1000	6500	142	50.4	−88	NA	21.6	31.8	10.20	2.3	12.2	9.90[f]
428	No	1000	9241	63	36.1	5	8	4.5	9.2	4.70[f]	1.3	< 1	−0.30[f]
431	No	1000	6104	610	129.9	584	NA	14.4	29.4	15.00	NA	NA	NA
471	Yes	1000A	6360	51	106	0	33	10.2	11.5	1.30[f]	7	6.1	−0.90[f]
433	Yes	1200	7631	231	25.1	21	8	8.4	19.5	11.10	8.5	18.6	10.10
437	No	1200	7632	28	140.3	15	336	8.4	8.4	0[f]	2.2	0.9	−1.30[f]
476[e]	No	1200A	4824	145	134.1	96	NA	< 1	2.3	1.30[f]	NA	NA	NA
446	No	1730	6955	42	46.4	−11	131	2.3	1.5	−0.80[f]	< 1	1.5	0.50[f]
447	Yes	1730	9202	13	68.7	0	28	1.3	1.7	0.40[f]	< 1	< 1	0[f]
450	Yes	1730	10,644	9	237.4	0	31	10.6	10.4	−0.20[f]	4.6	< 1	−3.60[f]
451	Yes	1730	4152	34	117.7	8	NA	16.9	29.5	12.60	11.6	23.2	11.60
453	No	1730	6955	41	223.7	27	NA	5.4	5.1	−0.30[f]	NA	NA	NA
456	Yes	1730	9065	13	196.7	0	32	14	14.1	0.10[f]	3.7	4.4	0.70[f]
457	Yes	1730	10,534	1	237.2	−2	17	12.6	15	2.40[f]	2	3	1[f]
460	No	2080	11,065	2	209.2	−5	NA	1.7	1.6	−0.1[f]	1	3	2[f]

ACTH: adrenocorticotropic hormone; Aldo: aldosterone; NA: not available.

[a] All patients have prostate carcinoma except for Patients 423 (breast), 446 (sarcoma), and 460 (sarcoma).

[b] Response for prostate carcinoma is defined as a 50% fall in prostate specific antigen from baseline, sustained for at least 3 consecutive weeks. For other carcinomas, Standard National Cancer Institute criteria were used.

[c] Normal range at the University of Chicago Adult Endocrinology Laboratory: 9–52 pg/mL.

[d] Difference between 0 minutes and 60 minutes after adrenocorticotropic hormone.

[e] Abnormal adrenal gland on computed tomography scan.

[f] Abnormal value.

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