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Research Article





INHIBITION OF ALDOSTERONE SECRETION AND MODIFICATION OF ELECTROLYTE EXCRETION IN MAN BY A CHEMICAL INHIBITOR OF 11β — HYDROXYLATION * †

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In 1958 it was shown by Chart and associates (1) that 2-methyl-1,2-bis-(3-pyridyl)-1-propanone (SU-4885) (Figure 1) when administered to dogs resulted in a striking, acute decrease in adrenocortical secretion of cortisol. Subsequent studies in the dog(2) and in man (3) indicated that SU-4885 inhibited the 11β-hydroxylation of corticosteroids so that 11-desoxycortisol (compound S) tended to replace cortisol and 11-desoxycorticosterone tended to replace corticosterone in the adrenal effluent. The ring-A saturated (tetrahydro-) metabolites of compound S and desoxycorticosterone (DOC) are not ordinarily present in measurable quantities in the urine, but during treatment with SU-4885 these steroids have been identified as major urinary steroids (3).

In man, cortisol is the adrenal hormone of principal importance in restraining adrenocorticotropic hormone (ACTH) secretion by the pituitary. By inducing a decrease in cortisol secretion, therefore, SU-4885 indirectly induces a measurable increase in ACTH secretion (4). Under the influence of high levels of ACTH the SU-4885-inhibited adrenal gland secretes large quantities of 11-desoxycorticosteroids (Figure 2).

The steroid patterns produced by SU-4885 are similar to those observed by Eberlein and Bongiovanni (5) in the hypertensive form of congenital adrenal hyperplasia, in which disease it is thought that 11β -hydroxylation is defective, leading to a relative or absolute deficiency of cortisol secretion, a compensatory increase in ACTH secretion, and

greatly excessive secretion of compound S, DOC and other 11-desoxysteroids.

Since aldosterone is hydroxylated in the 11β position, one might anticipate that its secretion would be inhibited by SU-4885 (Figure 3). A decrease in secretion of this important mineralocorticoid might be expected to lead to an increase in urinary sodium. The present report is concerned with a description of the effects of SU-4885 upon mineralocorticoid and electrolyte metabolism in man.

MATERIALS AND METHODS

Six normal young adults and nine hospitalized patients were studied while receiving diets which were constant from day to day. Complete 24 hour urine specimens, collected on ice or with thymol preservative, were analyzed within several hours after collection or were frozen until future analysis. SU-4885 was administered orally. Whenever steroids were employed they too were administered orally. Urinary aldosterone was measured by a modification of the method of Kliman and Peterson (6). Urinary pregnane-3,18,21-triol-11,20-dione was determined by a modification of the method of Ulick, Laragh and Lieberman (7). 17,21-Dihydroxy-20-ketosteroids (17-hydroxycorticoids) were determined by the method of Silber and Porter (8). 17-Ketosteroids were measured utilizing a color correction equation modified from Allen (9) applied to a methylene chloride extract of the Zimmermann chromogen developed by the procedure of Callow, Callow and Emmens (10) on urine ex-

Fig. 1. Chemical Structure of 2-methyl-1 2-bis-(3-pyridyl)-1-propanone (SU-4885)

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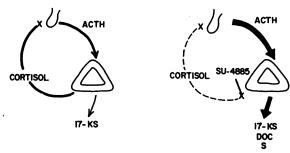


Fig. 2. SU-4885 Inhibition of Cortisol Results in "Compensatory" Increase in ACTH Secretion

ACTH in the presence of 11β -hydroxylase inhibition stimulates secretion of 11-desoxycorticosteroids such as 11-desoxycortisol (compound S) and DOC.

tracts prepared by the method of Drekter and associates (11). Steroid metabolites in the urine (tetrahydrocortisol, tetrahydrocortisone, tetrahydrodesoxycorticosterone and tetrahydro-compound S) were determined by methods previously described (3). Urinary chloride was determined by the potentiometric method of Sanderson (12). Sodium and potassium were analyzed by flame photometry. Urinary creatinine was determined by the method of Hawk, Oser and Summerson (13).

RESULTS

Regardless of the experimental conditions, SU-4885 consistently caused decreases in urinary aldosterone levels.

Fig. 3. Cortisol, Corticosterone and Aldosterone are all Hydroxylated in the 11β -Position and are Therefore Susceptible to SU-4885 Inhibition

In individuals with intact pituitary-adrenal function the administration of SU-4885 consistently resulted in the appearance of DOC in the blood and its metabolite tetrahydrodesoxycorticosterone in the urine. That this appearance of DOC was dependent upon increased secretion of ACTH has been shown previously (3) and was confirmed in this study by the fact that SU-4885 administration failed to result in the appearance of DOC in blood or urine when ACTH secretion was suppressed by prednisone or Dexamethasone.

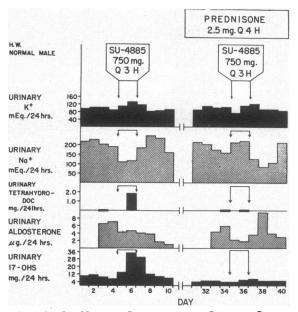


Fig. 4. In Normal Individual on Liberal Sodium Intake SU-4885 Alone Caused DOC Secretion with Sodium Retention and Potassium Loss

When prednisone was administered before and during SU-4885, no DOC was secreted and aldosterone inhibition was accompanied by sodium loss and potassium retention.

Effects of SU-4885 in normal subjects on a liberal sodium intake

Two normal individuals maintained on a constant high sodium intake received SU-4885. One of these subjects had a daily sodium intake of 200 mEq. and received SU-4885 750 mg. every three hours for two days. The second subject had a daily sodium intake of 100 mEq. and was given SU-4885 500 mg. every four hours for three days. Both studies are tabulated in Table I. Figure 4 illustrates the results of the first study.

When Subject H. W. received SU-4885 as his only treatment, tetrahydro-DOC, which had been

TABLE I

Effects of SU-4885* on urinary electrolytes and steroids in normal subjects on liberal sodium intake

Day	Treatment	Creatinine	Chloride	Potas- sium	Sodium	17-Hy- droxy- cortico- steroids	17-Keto- steroids	Aldo- sterone	Tetra- hydro- cortisone plus tetra- hydro- cortisol	Tetra- hydro- compound S	Tetra- hydro- desoxy- cortico- sterone
No.		mg./day		mEq./day	mEq./day	mg./day	mg./day	μg./day	mg./day	mg./day	mg./day
H.W.,	27, normal man; 200 m	Eq. sodium	diet								
1	0	1,860	204	97	222	10	12				
$\bar{2}$	Ö	1,790	206	102	230	11	7				
2 3	0	2,100	177	99	205	9	13	7	4.6	0	0
4	0	1,720	166	89	193	7	15	7			-
5 \SU	-4885, 750 mg. every	2,070	118	110	112	14	16	4			
	hrs.	2,080	103	136	117	35	29	4	4.0	13	1.8
7	0	1,960	168	118	187	30	28	4			
8	Ö	1,990	208	82	252	12	17	$\bar{4}$			
9	Ö	2,160	215	86	240	10	11	2			
10	0	2,050	163	92	161	8	8	1			
31	Prednisone 2.5 mg.	1,990	184	89	218	4	10				
32		2,100	190	110	207	5	7				
33	Prednisone every 4 hrs.	2,100	150	104	179	5	5	4			
34	Prednisone) 4 nrs.	1,960	131	108	160	4	5	6		0	0
35	Prednisone 2.5 mg.										
36	every 4 hrs. and SU-4885, 750 mg.	2,260	179	76	216	4	5	2			
00	every 3 hrs.	2,060	210	116	222	6	8	2		0	0
37	Prednisone 2.5 mg.	2,040	84	124	129	7	14	4			
38	Prednisone 2.5 mg.	2,000	82	94	86	5	7	10			
39	»everv	2.180	90	94	108	5	5	4			
40	Prednisone 4 hrs.	1,950	191	90	218	5	5	3			
J.J., 2	5, normal man; 100 mE	Eq. sodium d	iet								
1	0	2,480	186	125	103	14	14				
2	0	2,460	220	132	103	13	14				
2 3	0	2,330 2,380	188	116	96	13	14	22			
4	0	2,430	190	125	85	13	14	17	5.4	0	0
5) er		2,260	181	109	107	17	9	22			
6130	-4885, 500 mg. every	2,340	178	108	79	17	12	4			
7) '	l hrs.	2,460	184	135	91	30	19	4	5.7	8.2	1.3
8	0	2,560	180	114	101	14	14	21			
ğ	ŏ	2,220	194	114	109	12	10	18			
10	Ö	2,400	203	118	103	12	10				

^{*} SU-4885 = 2-methyl-1, 2-bis-(3-pyridiyl) 1-propanone.

too low to measure during control periods, rose to easily appreciable levels. Simultaneously, large quantities of tetrahydro-S appeared in the urine, accounting for a large increase in total 17-hydroxy-corticoid excretion. Associated with the increase in DOC and compound S secretion there was a significant decrease in urinary sodium and an increase in urinary potassium. Urinary aldosterone fell with SU-4885 administration. Presumably the sodium retention and potassium loss were consequences of the increase in DOC secretion.

A somewhat different response was observed when treatment with SU-4885 was repeated while H.W. was receiving prednisone as a suppressor of ACTH. Under these conditions SU-4885 did not induce the appearance of measurable quantities of tetrahydro-DOC or tetrahydro-S in the urine. Once again urinary aldosterone fell with SU-4885 administration. Sodium and chloride excretion increased and potassium excretion decreased, presumably as consequences of decreased aldosterone secretion.

TABLE II

Effects of SU-4885* and prednisone on urinary electrolytes and steroids in two normal subjects on constant 9 mEq. sodium diets

						17-Hy-			Pregnan-	Tetra- hydro- cortisone plus		Tetra-
Day	Treatment	Creatinine	Chloride	Potas- sium	Sodium	droxy- cortico-	17-Keto- steroids		3, 18, 21- triol-11, 20-dione	tetra-	Tetra- hydro- compound S	hydro- desoxy- cortico- sterone
No. H.V	V., 27, normal man	mg./day	mEq./day	mEq./day	mEq./day	mg./day	mg./day	μg./day	μg./day	mg./day	mg./day	mg./day
1 2 3 4	Prednisone Prednisone Prednisone Prednisone Prednisone	1,560 1,330 1,460 1,420	3 3 4 4	50 48 51 47	2 1 1 2	4 4 4 4	8 9 8 7	15 14 11 18	50 43 43 49	0.9	0	0
5 6 7	Prednisone 2.5 mg. every 8 hrs. and SU-4885, 500 mg. every 4 hrs.	1,470 1,730 1,460	5 6 7	39 81 83	10 7 15	5 12 12	8 11 13	6 6	10 11 0	1.8	5.7	0.9
8 9 10 11 12 13 14 15 16 17	Prednisone	1,430 1,880 1,260 1,480 1,500 1,415 1,440 1,430 1,375 1,690	8 6 5 6 8 6 5 5 5 5 5 5 5 5 5 5 5 5 5 5	67 47 46 60 71 56 51 50 52 51 57	7 4 3 3 4 4 2 3 7 5	8 4 4 5 3 3 3 2 2	8 8 7 7 5 5 5 5 7 5 9	8 15 15 15 14 9 15 15 13	37 45 42 50	0.13	0	0
19 20 21	Prednisone 2.5 mg. and SU-4885, 500 mg. every 4 hrs.	1,310 1,690 1,495	6 11 11	33 42 47	32 38 31	4 4 4	6 6 6	3 8 3	4 4 15	0.17	0	0
22 23 24 25	Prednisone Prednisone Prednisone Prednisone Prednisone	1,770 1,770 1,715 1,575	17 7 8 7	77 69 60 51	17 19 3 2	3 3 4 2	5 6 4 4	16 20 11 20	26 38			
J.J.,	25, normal man											
1 2 3 4 5 6 7 8	Prednisone Prednisone Prednisone Prednisone Prednisone Prednisone Prednisone Prednisone	1,810 1,716 1,760 1,610 2,120 2,680 2,440 1,760	13 8 11 8 8 6 6	112 104 137 112 121 125 136 107	7 2 3 1 2 1 2 2	7 7 8 9 8 7 7 5	11 5 9 8 7 9 7	72 47 79 62 59 39 62				
9 10 11	Prednisone 2.5 mg. every 4 hrs. and SU-4885, 500 mg.	2,230 1,950	14 9	111 91	11 5	13 10	11 11	23				
12 13 14 15 16 22 23 24 25	Prednisone	1,910 1,915 1,610 1,670 1,635 1,920 1,680 1,880 1,905	12 12 9 6 6 4 16 10 8 12	73 64 100 120 106 103 127 93 136	9 1 1 0.4 0.5 0.4 1 1 0.5	9 8 6 5 5 6 5 6	14 10 10 10 8 6 8 9 8	11 6 31 70 56 85 43 41 58		0.27	0	0
26 27 28	Prednisone 5 mg. every 4 hrs. and SU 4885, 500 mg.	1,850 1,950	9 21	78 103	3 25	6 8	7 7	25 8				
29 30 31	Prednisone Prednisone Prednisone Prednisone Prednisone	1,630 1,720 1,670	26 16 11	99 110 106	15 3 0.7	7 6 6	8 7 7	13 19 38		0.41	0	0
32	Prednisone 4 hrs.	1,800	13	124	0.5	8	7	68				

^{*} See footnote Table I.

When Subject J. J. received SU-4885 alone, tetrahydro-DOC and tetrahydro-S appeared in the urine in large quantities and once again there was a definite decrease in urinary aldosterone. Little change was noted in urinary sodium, chloride or potassium levels. Presumably in this particular study the rise in DOC secretion offset the fall in aldosterone with respect to effects on electrolyte excretion.

Effects of SU-4885 in normal subjects with high aldosterone levels secondary to low sodium intake

Restriction of dietary sodium in the normal individual has been shown to result in a decrease in urinary sodium and a rise in urinary aldosterone, which in our experience has been maintained for as long as sodium is rigidly withheld. One nor-

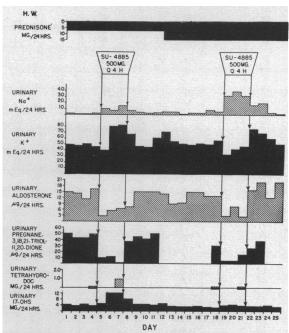


FIG. 5. URINARY STEROID AND ELECTROLYTE VALUES OF A NORMAL MAN MAINTAINED ON A CONSTANT LOW SODIUM DIET

During the first portion of the study prednisone in dosage of 2.5 mg. every eight hours failed to suppress completely the secretion of DOC in response to SU-4885. Although aldosterone levels fell, sodium diuresis was trivial and potassium excretion increased. During the second portion of the study prednisone in dosage of 2.5 mg. every four hours prevented secretion of DOC, so that as aldosterone levels fell there occurred a marked increase in urinary sodium accompanied by a decrease in urinary potassium.

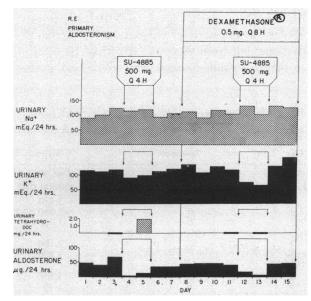


Fig. 6. In this Patient with Primary Aldosteronism SU-4885 Inhibition of Aldosterone was Associated with Potassium Retention

The effect was more marked when DOC secretion was precluded by Dexamethasone[®].

mal young woman taking a constant diet containing 9 mEq. of sodium per day was treated with SU-4885 in dosage of 500 mg. every four hours for two days. No ACTH suppressor was employed. During treatment with SU-4885 urinary tetrahydrodesoxycorticosterone rose from unmeasurable levels to 1.1 mg. per 24 hours. Urinary aldosterone fell from 21 μ g. prior to treatment to 6 μ g. per 24 hours on the first day and then rose again to 20 μ g. on the second day of treatment. No significant changes in urinary sodium or potassium were noted during SU-4885 administration.

Two other normal subjects on low sodium diet were studied while receiving prednisone as a suppressor of ACTH. The results are tabulated in Table II. Figure 5 illustrates one such study, which can best be considered in two parts. In the first half of the study the subject received only 7.5 mg. prednisone per day. That this was insufficient to suppress ACTH secretion completely is evidenced by the marked increase in urinary levels of tetrahydrodesoxycorticosterone and tetrahydro-compound S which occurred during treatment with SU-4885. Despite the fact that urinary aldosterone decreased from 18 μg. per 24 hours to

less than 3 μ g. per 24 hours and the urinary metabolite of aldosterone, pregnane-3,18,21-triol-11, 20-dione, fell from 49 μ g. to less than 10 μ g. per 24 hours, sodium diuresis was trivial and potas-

sium excretion increased during treatment with SU-4885.

During the second half of the study the dose of prednisone was increased to 15 mg. per day.

TABLE III

Effects of SU-4885,* with and without ACTH-suppressing steroids, in patients with secondary hyperaldosteronism

1 2 3 4 SU-4885, 756 6 7 J.W., 75, arterios 1 2 3 4 SU-4885, 506 6 7 J.M., 40, nephros 1 Prednisone 2 Prednisone 3 Prednisone 4 Prednisone 5 Prednisone 6 and 7 SU-4885, 5 8 Prednisone 10 Prednisone 11 Prednisone 12 Prednisone 12 Prednisone 12 Prednisone 13 A Dexameth	ec's cirrhosis, ascites; 22 mEq.	ml./day				
1 2 3 4 SU-4885, 756 6 7 J.W., 75, arterios 1 2 3 4 SU-4885, 506 6 7 J.M., 40, nephros 2 Prednisone 3 Prednisone 4 Prednisone 5 Prednisone 6 and 7 SU-4885, 5 8 Prednisone 10 Prednisone 11 Prednisone 12 Prednisone 12 Prednisone 12 Prednisone 14 Prednisone 15 Prednisone 16 Prednisone 17 SU-4885, 5 18 Prednisone 18 Prednisone 19 Prednisone 10 Prednisone 10 Prednisone 11 Prednisone 12 Prednisone 13 Prednisone 14 Dexameth 15 Dexameth 16 Dexameth			mEq./day	mEq./day	mg./day	mg./day
2 3 4 SU-4885, 756 6 7 J.W., 75, arterios 1 2 3 4 SU-4885, 506 6 7 J.M., 40, nephros 2 Prednisone 3 Prednisone 4 Prednisone 5 Prednisone 6 and 7 SU-4885, 5 8 Prednisone 10 Prednisone 11 Prednisone 12 Prednisone 12 Prednisone 12 Prednisone 14 Prednisone 15 Prednisone 16 Prednisone 17 Prednisone 18 Prednisone 19 Prednisone 10 Prednisone 10 Prednisone 11 Prednisone 12 Prednisone 13 Prednisone 14 Prednisone 15 Prednisone 16 Prednisone 17 Prednisone 18 Prednisone 19 Prednisone 10 Prednisone 10 Prednisone 11 Prednisone 12 Prednisone 13 Prednisone 14 Prednisone 15 Prednisone 16 Prednisone 17 Prednisone 18 Prednisone 19 Prednisone 10 Prednisone 10 Prednisone 11 Prednisone 12 Prednisone 13 Prednisone 14 Prednisone 15 Prednisone 16 Prednisone 17 Prednisone 18 Prednisone 18 Prednisone 19 Prednisone 10 Prednisone 10 Prednisone 10 Prednisone 10 Prednisone 10 Prednisone 11 Prednisone 12 Prednisone 13 Prednisone 14 Prednisone 15 Prednisone 16 Prednisone 16 Prednisone 17 Prednisone 18 Prednisone 18 Prednisone 19 Prednisone 10 Prednisone 10 Prednisone 10 Prednisone 10 Prednisone 11 Prednisone 12 Prednisone	•	sodium diet				
4 SU-4885, 756 6 7 J.W., 75, arterios 1 2 3 4 5 SU-4885, 506 6 7 J.M., 40, nephros 1 Prednisone 2 Prednisone 3 Prednisone 4 Prednisone 5 Prednisone 6 and 7 SU-4885, 5 8 Prednisone 10 Prednisone 11 Prednisone 12 Prednisone 12 Prednisone 12 Prednisone 13 Prednisone 14 Prednisone 15 Prednisone 16 Prednisone 17 Prednisone 18 Prednisone 19 Prednisone 10 Prednisone 10 Prednisone 11 Prednisone 12 Prednisone 13 Prednisone 14 Dexameth 15 Dexameth	0	3,350	97	5.7	7	1
4 SU-4885, 750 6 7 J.W., 75, arterios 1 2 3 4 SU-4885, 500 6 7 J.M., 40, nephros 1 Prednisone 2 Prednisone 4 Prednisone 5 Prednisone 6 and 7 SU-4885, 5 8 Prednisone 10 Prednisone 11 Prednisone 12 Prednisone 12 Prednisone 14 Prednisone 15 Prednisone 16 Prednisone 17 SU-4885, 5 18 Prednisone 19 Prednisone 10 Prednisone 11 Prednisone 12 Prednisone 12 Prednisone 13 Dexameth 14 Dexameth 15 Dexameth	0	2,940	75	4.4	6	2
J.W., 75, arterios 1 2 3 4 SU-4885, 500 6 7 J.M., 40, nephros 1 Prednisone 2 Prednisone 3 Prednisone 4 Prednisone 5 Prednisone 6 and 7 SU-4885, \$ 8 Prednisone 10 Prednisone 11 Prednisone 12 Prednisone 12 Prednisone 13 Prednisone 14 Prednisone 15 Prednisone 16 Prednisone 17 Prednisone 18 Prednisone 19 Prednisone 10 Prednisone 10 Prednisone 11 Prednisone 12 Prednisone 13 Prednisone 14 Dexameth 15 Dexameth	0	2,960	80	0.5	7	4
J.W., 75, arterios 1 2 3 4 SU-4885, 500 6 7 J.M., 40, nephros 1 Prednisone 2 Prednisone 3 Prednisone 4 Prednisone 5 Prednisone 6 and 7 SU-4885, \$ 8 Prednisone 10 Prednisone 11 Prednisone 12 Prednisone 12 Prednisone 13 Prednisone 14 Prednisone 15 Prednisone 16 Prednisone 17 Prednisone 18 Prednisone 19 Prednisone 10 Prednisone 10 Prednisone 11 Prednisone 12 Prednisone 13 Prednisone 14 Dexameth 15 Dexameth	(O mag arrams 4 hm	2,100	47	1.3	18	3
J.W., 75, arterios 1 2 3 4 SU-4885, 500 6 7 J.M., 40, nephros 1 Prednisone 2 Prednisone 4 Prednisone 5 Prednisone 6 and 7 SU-4885, 5 8 Prednisone 9 Prednisone 10 Prednisone 11 Prednisone 12 Prednisone 12 Prednisone 14 Prednisone 15 Prednisone 16 Prednisone 17 SU-4885, 5 18 Prednisone 18 Prednisone 19 Prednisone 10 Prednisone 10 Prednisone 11 Prednisone 12 Prednisone 13 Dexameth 14 Dexameth 15 Dexameth	o mg. every 4 nrs.	2,200	73	1.5	36	8
J.W., 75, arterios 1 2 3 4 SU-4885, 500 6 7 J.M., 40, nephros 1 Prednisone 2 Prednisone 4 Prednisone 5 Prednisone 6 and 7 SU-4885, 5 8 Prednisone 10 Prednisone 11 Prednisone 12 Prednisone 12 Prednisone 14 Prednisone 15 Prednisone 16 Prednisone 17 SU-4885, 5 18 Prednisone 18 Prednisone 19 Prednisone 10 Prednisone 10 Prednisone 11 Prednisone 12 Prednisone 12 Prednisone 13 Dexameth 15 Dexameth	0	2,850	80	0.6	11	7
1 2 3 4 5 SU-4885, 500 6 7 J.M., 40, nephros 1 Prednisone 2 Prednisone 3 Prednisone 4 Prednisone 5 Prednisone 6 and 7 SU-4885, \$ 8 Prednisone 10 Prednisone 11 Prednisone 12 Prednisone 12 Prednisone 14 Prednisone 15 Prednisone 16 Prednisone 17 Prednisone 18 Prednisone 19 Prednisone 10 Prednisone 10 Prednisone 11 Prednisone 12 Prednisone 13 Prednisone 14 Dexameth 15 Dexameth	Ō	3,195	78	0.5	7	4
2 3 4 5 SU-4885, 500 6 7 I.M., 40, nephros 2 Prednisone 2 Prednisone 3 Prednisone 4 Prednisone 5 Prednisone 6 and 7 SU-4885, 3 8 Prednisone 9 Prednisone 10 Prednisone 11 Prednisone 12 Prednisone 12 Prednisone 13 Prednisone 14 Prednisone 15 Prednisone 16 Prednisone 17 Prednisone 18 Prednisone 19 Prednisone 10 Prednisone 10 Prednisone 11 Prednisone 12 Prednisone 13 Prednisone 14 Dexameth 15 Dexameth	sclerotic heart disease, edema;	22 mEq. sod	lium diet			
4 SU-4885, 500 6 7 I.M., 40, nephrose 1 Prednisone 2 Prednisone 3 Prednisone 4 Prednisone 5 Prednisone 6 and 7 SU-4885, \$ 8 Prednisone 10 Prednisone 11 Prednisone 12 Prednisone 12 Prednisone 13 Prednisone 14 Prednisone 15 Prednisone 16 Prednisone 17 Prednisone 18 Prednisone 19 Prednisone 10 Prednisone 10 Prednisone 11 Prednisone 11 Prednisone 12 Prednisone 13 Dexameth 15 Dexameth	. 0	1,160	42	29	6	4
4 SU-4885, 500 6 7 6 7 7 7 7 7 8 8 9 8 8 9 8 9 9 8 9 9 9 9 9	. 0	1,400	28	31	4	2
6 7 7 7 7 7 7 7 7 8 7 8 8 8 9 8 7 8 8 9 8 9	Ŏ	2,225	42	28	6	3
6 7 M., 40, nephros 1 Prednisone 2 Prednisone 3 Prednisone 4 Prednisone 5 Prednisone 6 and 7 SU-4885, \$ 8 Prednisone 9 Prednisone 10 Prednisone 11 Prednisone 12 Prednisone 12 Prednisone 14 Prednisone 15 Prednisone 16 Prednisone 17 Prednisone 18 Prednisone 19 Prednisone 10 Prednisone 10 Prednisone 11 Prednisone 12 Prednisone 12 Prednisone 13 Prednisone 14 Dexameth 15 Dexameth		1,750	47	9	10	4
7 I.M., 40, nephros 1 Prednisone 2 Prednisone 3 Prednisone 4 Prednisone 5 Prednisone 6 and 7 SU-4885, \$ 8 Prednisone 9 Prednisone 10 Prednisone 11 Prednisone 12 Prednisone 12 Prednisone 14 Prednisone 15 Dexameth 1 Dexameth 1 Dexameth	0 mg. every 4 hrs.	2,160	57	Ź	20	4
7 1.M., 40, nephros 2. Prednisone 3. Prednisone 4. Prednisone 5. Prednisone 6. and 7. SU-4885, 3. 8. Prednisone 9. Prednisone 10. Prednisone 11. Prednisone 12. Prednisone 12. M., 36, postnec 12. 3 4. Dexameth 5. Dexameth	0	1,950	77	20	28	9
1 Prednisone 2 Prednisone 3 Prednisone 4 Prednisone 5 Prednisone 6 and 7 SU-4885, \$ 8 Prednisone 9 Prednisone 10 Prednisone 11 Prednisone 12 Prednisone 12 Prednisone 14 Dexameth 5 Dexameth	Ŏ	750	38	9	20	$\overset{\checkmark}{4}$
1 Prednisone 2 Prednisone 3 Prednisone 4 Prednisone 5 Prednisone 6 and 7 SU-4885, \$ 8 Prednisone 9 Prednisone 10 Prednisone 11 Prednisone 12 Prednisone 12 Prednisone 14 Prednisone 15 Prednisone 16 Prednisone 17 Prednisone 18 Prednisone 19 Prednisone 10 Prednisone 10 Prednisone 11 Prednisone 12 Prednisone 12 Prednisone 13 Prednisone 14 Dexameth 15 Dexameth	sis, edema; 22 mEq. sodium d	iet				
2 Prednisone 3 Prednisone 4 Prednisone 5 Prednisone 6 SU-4885, 3 8 Prednisone 9 Prednisone 10 Prednisone 11 Prednisone 12 Prednisone 12 Prednisone 14 Dexameth 5 Dexameth	· ·	2.000	72	12		
4 Prednisone 5 Prednisone 6 and 7 SU-4885, 3 8 Prednisone 9 Prednisone 10 Prednisone 11 Prednisone 12 Prednisone 12 Prednisone 1 Predni	le l	1,500	40	9		
4 Prednisone 5 Prednisone 6 and 7 SU-4885, 3 8 Prednisone 9 Prednisone 10 Prednisone 11 Prednisone 12 Prednisone 1 Prednisone	5 mg. every 8 hrs.	1,710	30	ģ		
6 and 7 SU-4885, S 8 Prednisone 9 Prednisone 10 Prednisone 11 Prednisone 12 Prednisone 1.M., 36, postnee 1 2 3 4 Dexameth 5 Dexameth		1,770	34	11		
6 and 7 SU-4885, S 8 Prednisone 9 Prednisone 10 Prednisone 11 Prednisone 12 Prednisone 1.M., 36, postnee 1 2 3 4 Dexameth 5 Dexameth	e, 5 mg every 8 hrs.	1,310	28	10		
7 SU-4885, 5 8 Prednisone 9 Prednisone 10 Prednisone 11 Prednisone 12 Prednisone 1	.,	1,920	34	20		
9 Prednisone 10 Prednisone 11 Prednisone 12 PrednisoneM., 36, postnec 1 2 3 4 Dexameth 5 Dexameth	500 mg. every 4 hrs.	2,110	33	32		
9 Prednisone 10 Prednisone 11 Prednisone 12 PrednisoneM., 36, postnec 1 2 3 4 Dexameth 5 Dexameth	. · ·	1,760	34	28		
10 Prednisone 11 Prednisone 12 PrednisoneM., 36, postnee 1 2 3 4 Dexameth 5 Dexameth		1,550	37	18		
11 Prednisone 12 Prednisone M., 36, postner 1 2 3 4 Dexameth 5 Dexameth		1,670	27	16		
12 Prednisone M., 36, postner 1 2 3 4 Dexameth 5 Dexameth		1,530	44	11		
1 2 3 4 Dexameth 5 Dexameth		1,650	54	12		
1 2 3 4 Dexameth 5 Dexameth	ecrotic cirrhosis, ascites; 22 mE	Ea. sodium di	et			
2 3 4 Dexameth 5 Dexameth	0	1,180	64	0.2	2	1
4 Dexameth 5 Dexameth	ŏ	1,260	68	0.2	$\tilde{2}$	$\bar{2}$
5 Dexameth	Ŏ	1,520	65	0.2	3	1
5 Dexameth	aggaraR)	1,480	94	0.3	3	1
	nasone ¹ 0.5 mg. every 8 hrs.	1,460	66	0.3	ĭ	ī
		1,290	69	0.3	$\tilde{2}$	ī
7 Dexameth	•	1,350	61	5.4	2	1
8 Dexametri	nasone ^R 0.5 mg. every 8 hrs.	1,510	73	7.6	2	2
	750 mg. every 3 hrs.	1,385	60	7.5	3	ĩ
10 Dexameth		1.085	55	1.6	1	1
	vacamaR1		60	0.7	2	i
12 Dexameth	nasone ^R	1 4/15		U. 1	~	
13 Dexameth	nasone ^R nasone ^R nasone ^R 0.5 mg. every 8 hrs.	1,345 1,100	35	0.5	2	1

^{*} See footnote, Table I.

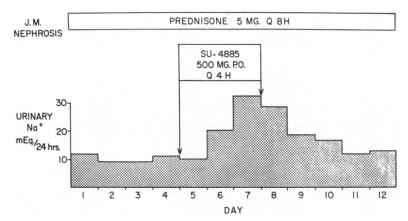


FIG. 7. IN THIS PATIENT WITH NEPHROSIS AND SECONDARY HYPERALDO-STERONISM, SU-4885 INHIBITION OF ALDOSTERONE RESULTED IN SODIUM DIURESIS WHEN DOC SECRETION WAS PREVENTED BY PREDNISONE

This time no tetrahydrodesoxycorticosterone was measurable in the urine either before or during SU-4885 treatment. Once more SU-4885 induced a striking fall in urinary aldosterone and pregnane-3,18,21-triol-11,20-dione; this time the fall in aldosterone was accompanied by an unequivocal increase in urinary sodium and decrease in urinary potassium.

Effects of SU-4885 in a patient with primary hyperaldosteronism

The effect of SU-4885 was studied in one patient with primary hyperaldosteronism, proven at operation to be due to a benign adrenocortical adenoma (Figure 6). The patient was a 32 year old woman with hypertension, cardiac arrhythmias, and hypokalemia despite potassium supplements. On a constant diet containing 100 mEq. sodium and 128 mEq. potassium, here urinary aldosterone averaged 49 μ g. per 24 hours. In the absence of any ACTH suppressors, SU-4885 in dosage of 500 mg. every four hours for two days resulted in a striking fall in aldosterone to 4 µg. per day and a rise in tetrahydrodesoxycorticosterone to 1.9 mg. per day. Urinary potassium decreased slightly.

In a subsequent portion of the study the patient was given Dexamethasone[®] 0.5 mg. every eight hours as a suppressor of ACTH. Again a marked fall in urinary aldosterone was observed during treatment with SU-4885 but this time a measurable quantity of tetrahydrodesoxycortico-

sterone failed to appear in the urine. Urinary potassium fell sharply during treatment with SU-4885 and rose again following withdrawal of SU-4885. Despite the impressive effect of SU-4885 on urinary aldosterone and potassium, no appreciable change in urinary sodium occurred.

Effects of SU-4885 in patients with secondary hyperaldosteronism

Four patients with secondary hyperaldosteronism and edema have been studied (Table III). In Patient L.T., a man with Laennec's cirrhosis, ascites, and marked sodium retention, the administration of SU-4885 without any ACTH suppressor caused urinary potassium to fall from 80 mEq. per day to 47 mEq. per day, but urinary sodium did not change significantly. In Patient J.W., a man with arteriosclerotic heart disease and edema, sodium retention occurred in response to SU-4885 administered in the absence of any suppressors of ACTH. Two edematous patients, J.M. and L.M., were receiving ACTH-suppressing steroids when SU-4885 was administered. In both cases treatment with SU-4885 resulted in a significant increase in sodium excretion (Figure 7). In patients with secondary hyperaldosteronism and near-maximal tubular reabsorption of sodium the SU-4885-induced increase in sodium excretion has sometimes been as much as 20-fold over baseline excretion, but even this has not constituted enough of a diuresis to be worthwhile from the standpoint of clinical therapy.

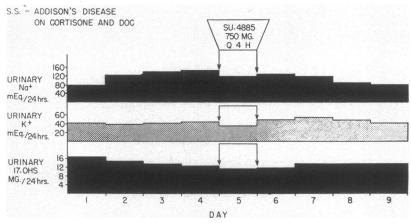


FIG. 8. LACK OF EFFECT OF SU-4885 IN PATIENT WITH ADDISON'S DISEASE
This patient was maintained on a constant high sodium diet, cortisone acetate
50 mg. (intramuscular) daily and DOC-trimethylacetate 50 mg. (intramuscular)
every four weeks.

SU-4885 administration in Addison's disease

If it is assumed that the effects of SU-4885 on sodium and potassium excretion are the manifestations of altered mineralocorticoid metabolism due to inhibition of adrenocortical 11β-hydroxylase, the presence of the adrenal cortex is a requisite for its action. To exclude the possibility that SU-4885 might have some extra-adrenal electrolyte-regulating function, it was given to a bilaterally adrenalectomized patient maintained on salt, cortisone and DOC-trimethylacetate (Figure 8). There was no significant change in urinary sodium, potassium, 17-hydroxycorticoids or 17-ketosteroids.

DISCUSSION

SU-4885 is a potent inhibitor of 11β-hydroxylation of adrenal steroids. By inhibiting 11β-hydroxylation it interferes with the secretion of three major adrenal steroids—cortisol, corticosterone and aldosterone. The level of circulating cortisol controls ACTH release. Therefore a "compensatory" increase in ACTH secretion occurs as a consequence of the SU-4885-induced decrease in cortisol secretion. In the dosages employed in this study SU-4885 does not completely block 11β-hydroxylation, so that under the influence of high levels of ACTH the secretion of cortisol gradually (within a day or so) returns to normal. At the same time, however, the high levels of ACTH acting upon the SU-4885-inhibited adrenals bring

about the secretion of compound S and desoxycorticosterone at rates far beyond the normal range. Compound S has neither significant glucocorticoid nor mineralocorticoid activity (14), but DOC is a potent mineralocorticoid. SU-4885 treatment of individuals with normal pituitary function results, then, in inhibition of one mineralocorticoid, aldosterone, and enhanced secretion of another, desoxycorticosterone. When DOC secretion predominates, sodium retention and potassium loss occur. When aldosterone inhibition predominates, sodium loss and potassium retention occur. The net effect of SU-4885 on electrolytes represents the algebraic sum of its DOC-promoting and aldosterone-inhibiting actions.

The inhibition of aldosterone by SU-4885 is a primary effect, *i.e.*, a consequence of direct action of the compound on the adrenal cortex and not merely a secondary compensation for DOC-induced sodium retention, for it was observed in every instance, whether or not DOC was concomitantly being secreted and whether or not sodium retention occurred. Conceivably, a decrease in aldosterone secretion might also occur in part as an *indirect* effect whenever SU-4885-induced secretion of DOC results in significant sodium retention.

In order to study the effects of SU-4885 upon aldosterone secretion it was necessary to establish conditions that would preclude the secretion of large amounts of DOC in response to SU-4885. At this point advantage was taken of the fact that

aldosterone secretion and DOC secretion are regulated through different mechanisms. DOC secretion is under the influence of ACTH, whereas aldosterone secretion is regulated by an extrapituitary mechanism (15). When sufficient amounts of ACTH-suppressing steroids such as prednisone or Dexamethasone® were given, DOC secretion was precluded; aldosterone secretion remained unaffected, however, and it became possible to study the effect of the 11β -hydroxylase inhibitor upon aldosterone secretion as an isolated phenomenon.

It is noteworthy that inhibition of aldosterone secretion by SU-4885 caused sodium loss and potassium retention in a normal individual on a liberal sodium diet (Figure 4) as well as in those. on low sodium diets. The thesis that aldosterone may have an appreciable effect upon renal function in the normal individual on liberal sodium intake has found independent support in studies with the steroid-17-spirolactones (16). "aldosterone antagonists" induce sodium loss only in the presence of aldosterone or aldosterone-like steroids (17). They are without effect in patients with untreated Addison's disease but have appreciable effect in normal individuals or patients with Addison's disease who are pretreated with DOC. The effects are most conspicuous in individuals who are secreting large amounts of aldosterone but are also appreciable in normal individuals in whom only small amounts of aldosterone are being secreted owing to a liberal intake of sodium.

In patients with secondary hyperaldosteronism associated either with dietary sodium restriction or pathological "edema-forming" states, SU-4885 had little effect upon sodium or potassium excretion in the absence of ACTH suppression. Presumably the inhibition of aldosterone synthesis did not, under these conditions, lead to sodium diuresis because large quantities of DOC were secreted in response to SU-4885. The concurrent administration of ACTH-suppressive steroids with SU-4885 allowed aldosterone inhibition to predominate and led to sodium diuresis and potassium retention (Figures 5, 7).

The failure of sodium diuresis to occur after SU-4885, even with ACTH suppression, in the patient with primary hyperaldosteronism is of considerable interest. This patient also responded to

the steroid-17-spirolactones with conspicuous potassium retention and relatively little sodium diuresis, whereas most individuals show principally sodium diuresis in response to the "aldosterone antagonists."

SUMMARY

- 1). 2-Methyl-1,2-bis-(3-pyridyl)-1-propanone (SU-4885) is a potent inhibitor of 11β -hydroxylation of steroids in man.
- 2). As a result, SU-4885 interferes with adrenocortical synthesis and secretion of three major adrenal steroids—cortisol, corticosterone and aldosterone.
- 3). Since cortisol controls adrenocorticotropic hormone (ACTH) release, administration of SU-4885 gives rise to a compensatory increase in ACTH.
- 4). In the presence of inhibition of 11β -hydroxylation, ACTH promotes secretion of desoxycorticosterone (DOC) and 11-desoxycortisol, the former a potent mineralocorticoid.
- 5). The net effect of SU-4885 on electrolyte excretion is the algebraic sum of its DOC-promoting and aldosterone-inhibiting activities.

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