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INHIBITION BY ESTROGEN ADMINISTRATION OF ADRENAL-PITUITARY RESPONSE TO METHOPYRAPONE*

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Recent studies carried out in this laboratory have shown a potentiating effect of estrogen therapy on the biologic activity of administered hydrocortisone (1). The glucosuric effect of exogenous hydrocortisone was much greater when ethinyl estradiol (EE) was administered together with the steroid, while a potentiating effect was not clearly demonstrated with a number of 1,2-unsaturated steroids. Estrogen therapy has been shown to increase the plasma levels of 17-hydroxycorticoids (2, 3) owing to an increase in the levels of transcortin (CBG, corticosteroid-binding globulin) (4, 5), but such a change does not occur in urinary corticoids, which may show a decrease (6).

In the present study, an attempt was made to determine whether estrogen therapy affects the pituitary-adrenal response in man.

METHODS

Eleven patients were studied in the metabolic ward of the Los Angeles County General Hospital. Table I shows age, sex, diagnosis, and duration of EE treatment. Each subject acted as his own control. Methopyrapone (2-methyl-1,2-bis-[3-pyridyl]-propanone) was given orally to these patients in doses of 500 or 750 mg every 4 hours for 2 days during the control period. The same doses were repeated during EE administration. The response to methopyrapone was estimated as urinary 17-ketogenic steroids (17-KGS) by the method of Rutherford and Nelson (7) in 24-hour collections the day before, during, and the day after drug administration. Twenty-four-hour urinary creatinine was measured as a check on the completeness of collections. An ACTH stimulation test was performed in six patients before and during EE administration, and in one additional patient no control infusion was performed. For the test, 50 IU of ACTH was given intravenously for exactly 8 hours for 2 successive days, and urinary 17-KGS were measured on both days. An average of 4 days was allowed between the methopyrapone and ACTH tests in each patient.

RESULTS

As can be seen in Table II, the urinary 17-KGS excretion the day after methopyropone administration increased in all eleven patients, with a mean increase of 41.7 mg per 24 hours during the control period. The day after methopyrapone therapy was chosen for tabulation, since urinary 17-KGS were generally highest on this day, although proportionate increases occurred on all days of methopyrapone administration. During EE administration, the mean increase was only 10.9 mg in 24 hours, a value significantly different ($p < .02$) from the response during the control period. Two

TABLE I

Summary of treatment with ethinyl estradiol

Patient	Age	Sex	Diagnosis	EE duration*
	years			*days*
1	59	M	Diabetes	9
2	35	F	Obesity	7
3	62	M	Diabetes	11
4	62	M	Diabetes	49
5	24	F	Turner's syndrome	7
6	28	F	Turner's syndrome	6
7	47	F	Diabetes	31
8	37	F	Normal	10
9	52	M	Diabetes	10
10	28	F	Normal	12
11	30	F	Hypothyroid	7

* EE = ethinyl estradiol, 0.05 mg twice a day.

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TABLE II

Response to methopyrapone before and during estrogen administration

Patient	Methopyrapone	Urinary 17-ketogenic steroids: Day before methopyrapone −EE*	Day before methopyrapone +EE	Day after methopyrapone −EE	Day after methopyrapone +EE	Difference −EE	Difference +EE
	mg/4 hours × 2 days	*mg/day*		*mg/day*		*mg/day*	
1	500	10.9	9.7	23.6	9.4	12.7	−.3
2	750	16.8	17.0	45.5	24.6	28.7	7.6
3	750	6.7	5.1	60.2	5.7	53.5	.6
4	500	10.1	8.8	18.2	10.2	8.1	1.4
5	500	5.6	4.4	40.3	11.0	34.7	6.6
6	500	5.6	9.6	36.5	31.6	30.9	22.0
7	500	5.2	4.3	16.3	9.2	11.1	4.9
8	750	11.8	7.5	147.0	8.8	135.2	1.3
9	750	13.0	6.8	63.4	13.1	50.4	6.3
10	500	8.0	1.8	55.3	21.4	47.3	19.6
11	500	8.7	4.5	54.9	54.6	46.2	50.1
				Mean		41.7	10.92
				SE		10.6	4.5
				p		<0.02	

* −EE = without ethinyl estradiol; +EE = with ethinyl estradiol, 0.05 mg twice a day.

patients showed a normal response to methopyrapone, four (Patients 1, 3, 4, and 8) showed no response, and five showed a marked decrease. Duration of treatment with EE was not clearly correlated with response. Although Patients 6 and 11, who did not show the expected effect, had been receiving EE for a relatively short time, a complete inhibition of response was achieved in Patients 1, 2, and 5, who also received treatment for a short time. In Patient 11, methopyrapone was repeated after 18 days of EE administration, and the response was similar to that seen on day 7 of treatment. To check the importance of individual variation, Patient 3 was studied again 28 days after EE was discontinued and, as Figure 1 shows, responded normally.

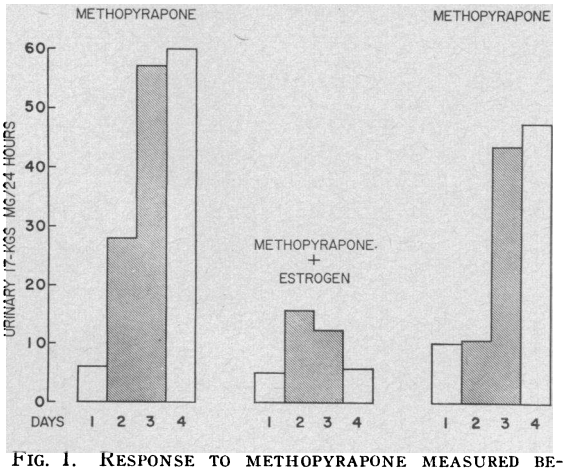

FIG. 1. RESPONSE TO METHOPYRAPONE MEASURED BEFORE, DURING, AND 28 DAYS AFTER 0.1 MG ETHINYL ESTRADIOL DAILY FOR 11 DAYS (PATIENT 3). Shaded areas represent days on which 750 mg methopyrapone was given every 6 hours.

TABLE III

Response to ACTH stimulation before and during ethinyl estradiol (EE) administration

Patient	Days of ACTH	Urinary 17-ketogenic steroids: Control	During EE
		mg/day	*mg/day*
9	1		37.8
	2		40.7
6	1	20.7	23.9
	2	36.3	37.5
8	1	73.8	40.7
	2	104.7	50.8
10_1	1	70.7	50.7
	2	58.5	63.8
10_2	1		37.0
	2		67.3
11	1	47.2	48.2
	2	35.0	37.0
E.C.	1	81.1	95.5
	2	89.7	169.9
T.M.	1	32.8	24.6*
	2	53.0	51.7

* Corrected for creatinine value.

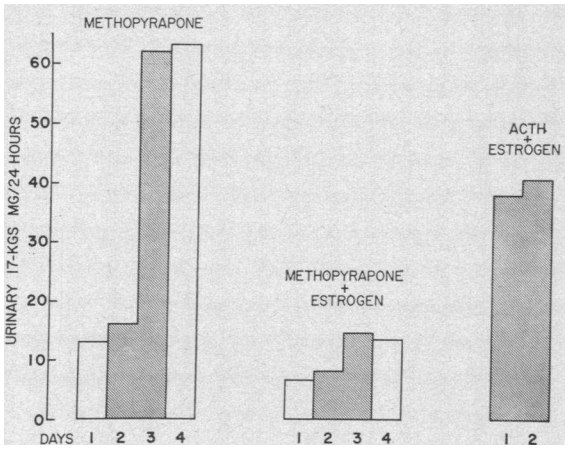

FIG. 2. RESPONSE TO METHOPYRAPONE BEFORE AND DURING ESTROGEN THERAPY, AND TO ACTH DURING ESTROGEN THERAPY (PATIENT 9). Methopyrapone was given on days 8 and 9 of therapy and ACTH on days 12 and 13. Shaded areas represent days of ACTH or methopyrapone administration.

The response to ACTH stimulation was studied in seven patients during EE administration, and all responded virtually normally (Table III). Figures 2 and 3 show the response in two such patients. An ACTH stimulation test was done in Patient 10 twice while she was on EE therapy, and both responses were similar to that of the control period (Figure 3).

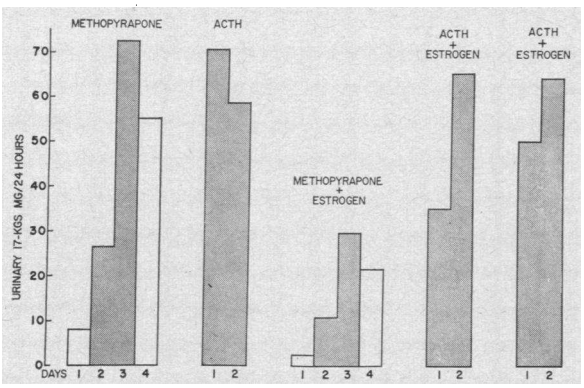

FIG. 3. RESPONSE TO METHOPYRAPONE AND ACTH BEFORE AND DURING ESTROGEN ADMINISTRATION (PATIENT 10). ACTH was given 3 days after methopyrapone during the control period. Methopyrapone was given again on days 12 and 13 of ethinyl estradiol administration, and ACTH on days 16 and 17 of estrogen treatment. Shaded areas represent days of ACTH or methopyrapone administration.

DISCUSSION

Estrogen effect on the pituitary-adrenal axis has been studied by a number of investigators in animals. In the rat, Vogt (8, 9) and Holzbauer (10) demonstrated that there is a decrease in corticosterone secretion by the adrenal gland when hexestrol is administered. Many years before, Korenchevsky and Dennison (11) found that during estrogen administration a consistent increase in adrenal size occurred. The following year, Selye and Collip (12) demonstrated that such an effect is dependent on a functioning pituitary gland. This effect on corticosterone production has been confirmed in *in vitro* studies by McKerns (13).

Taliaferro, Cobey, and Leone (2) and Wallace, Silverberg, and Carter (3) have described an increase in plasma 17-hydroxycorticosteroids in patients receiving estrogen, and a similar increase in pregnant women was demonstrated by Gemzell (14). This elevated level of plasma corticoids depends on an increased plasma level of transcortin (4, 5). These elevated plasma 17-hydroxycorticoids were presumed to be biologically inactive because estrogen-treated patients presented none of the clinical features of Cushing's syndrome, because with these high plasma levels there was no increase in the glucosuria in diabetic patients (1), and finally, because, by the demonstration of Slaunwhite, Lockie, Back, and Sandberg (15), addition of transcortin to an *in vivo* system blocks cortisone effect.

Plasma 17-hydroxycorticosteroids after EE administration have been studied in detail by several workers (3, 6) who showed an augmented response to exogenous ACTH during EE administration in doses of 0.1 mg per day. In addition, Marks, Friedman, and Duncan (16) and Robertson, Stiefel, and Laidlaw (17) demonstrated similar changes in plasma corticoids and normal response of urinary 17-hydroxycorticosteroids when ACTH was administered to patients receiving estrogen.

An increase in hydrocortisone half-life was demonstrated by Wallace and associates (3) and Peterson, Nokes, Chen, and Black (6) in patients receiving EE, and in pregnant patients by Cohen, Stiefel, Reddy, and Laidlaw (18) and Migeon, Bertrand, and Wall (19). Nelson, Tanney, Mest-

man, Gieschen, and Wilson (1) showed that administration of EE increases the biologic activity of exogenous hydrocortisone. This effect was thought possibly to be the result of altered corticoid metabolism, but this was not established by the data presented.

The mechanism of the observed effect of estrogen on response to methopyrapone is not clear, but the results may possibly be explained by one or a combination of the following mechanisms. *1) Inhibition of adrenal ability to secrete corticosteroids under ACTH stimulation.* This possibility is almost ruled out by the response of such patients to exogenous ACTH stimulation. It is conceivable, however, that the amount of ACTH needed for maximal adrenal response is much greater in patients receiving EE. Under these conditions, the response of endogenous ACTH to methopyrapone would not be great enough to produce an increase in corticoid secretion by the adrenal, while the excess ACTH given exogenously for the test could produce a response.

2) Inhibition of ACTH secretion. The response of these patients to ACTH stimulation suggests that the estrogen effect is not at the adrenal level, but appears to be in connection with ACTH release from the pituitary. Gemzell's finding (20) of an increase in plasma ACTH in rats treated with estrogen may be secondary to decreased ability of the adrenal to secrete corticoids, known to occur after large doses of estrogen. Vogt (8, 9) demonstrated decreased corticosterone secretion in estrogen-treated rats, and similar findings were shown in humans by Peterson and associates (6), which could have resulted from a decrease in ACTH production, but also could represent decreased ability of the gland to produce corticoids.

3) Increase in CBG acts to suppress ACTH output. Although the studies previously mentioned indicated that corticoids bound to transcortin generally are biologically inactive, the possibility that an increase in circulating concentration of such corticoids during EE treatment could inhibit the release of ACTH from the pituitary should be taken into consideration. On this basis, the decrease in corticosteroid output by the adrenals (6) could be explained. Pregnancy produces many of the features seen in patients during estrogen therapy, such as elevation of plasma 17-hydroxycorticosteroids and transcortin, prolongation in hydrocortisone half-life, and difference in glucosuric effect between hydrocortisone and prednisolone (21). Brownie and Sprunt (22) have reported three pregnant patients who had a diminished response to methopyrapone. It seems possible that this effect in pregnancy depends on the high levels of circulating estrogen present in these patients.

4) Prolongation of the hydrocortisone half-life. As previously mentioned, EE delays hydrocortisone's disappearance from the circulation. This effect could be dependent on the rise in plasma transcortin, or a diminished transformation of cortisol to certain of its metabolites by the liver, or both. EE has been shown to change the ratio of conjugate to free urinary 17-hydroxycorticoids, with a decrease in the former and no change or a small increase in the latter (5). An increase in hydrocortisone half-life from a normal of 60 to 111 minutes to a value of 114 to 205 minutes has been reported by Mills, Schedl, Chen, and Bartter (23). Recently, Wynn, Landon, and James (24) have shown that administration of methandienone (Dianabol) also inhibits the response to methopyrapone; it also increases hydrocortisone half-life (25), but does not produce an increase in plasma transcortin. These investigators found an alteration in liver function in five out of eight patients, which may be responsible for the increased plasma corticosteroid half-life seen with this substance.

The data presented do not clearly differentiate between the relative effects of the mechanisms above in producing inhibition of response to methopyrapone in patients treated with estrogenic substances. Prolongation of hydrocortisone half-life in the circulation by estrogen treatment might be sufficient explanation for the findings. If the biologic effect of the small amount of cortisol produced by the adrenal gland during methopyrapone administration is potentiated by increased circulation time, it seems likely that less ACTH would be produced, and thus a decreased urinary 17-KGS response would result. Contrary to this hypothesis, however, is the report of Liddle and associates (26) that patients with hypothyroidism who also have a prolongation of cortisol half-life (27–29) respond normally to oral methopyrapone. Brownie and Sprunt (22) and Brinck-

Johnsen, Solem, Brinck-Johnsen, and Ingvaldsen (30), however, failed to demonstrate a normal response to methopyrapone in a smaller group of hypothyroid patients.

SUMMARY

Eleven patients were given methopyrapone orally before and during estrogen therapy in an attempt to see whether estrogen affects the pituitary-adrenal response in man. Nine out of eleven patients showed a decreased response in urinary 17-ketogenic steroids during estrogen therapy. The mean increase in all eleven patients during the control period was 41.7 mg per 24 hours the day after methopyrapone. During estrogen therapy, the mean increase was only 10.9 mg in 24 hours, a value significantly different ($p < .02$) from the response during the control period. Exogenous ACTH produced a normal response in seven patients studied during estrogen therapy. Several possibilities for the mechanism of the observed effect of estrogen on such a response have been discussed.

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