CORTICOSTEROID-INDUCED HYPOTHALAMO-PITUITARY-ADRENAL AXIS SUPPRESSION

PROSPECTIVE STUDY USING TWO REGIMENS OF CORTICOSTEROID THERAPY

BY

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Long-term oral corticosteroid therapy leads to suppression of the hypothalamo-pituitary-adrenal (HPA) axis (Paris, 1961; Treadwell, Savage, Sever, and Copeman, 1963; Jasani, Boyle, Greig, Dalakos, Browning, Thompson, and Buchanan, 1967). Much work has been done on the influence of the regimen of corticosteroid administration on this suppression. Harter, Reddy, and Thorn (1963) have presented evidence that administration of oral corticosteroid in a single dose given every other day leads to substantially less adrenal suppression than that which occurs with a regimen giving divided doses of corticosteroid over the same period. The doses used in this study were not physiological; that is to say patients received doses of prednisone or prednisolone-equivalent ranging from 20 to 40 mg. daily. Grant, Forsham, and DiRaimondo (1965) have shown that a daily morning dose of 8 mg. Triamcinolone administered to normal subjects over a period of 8 days does not lead to lasting adrenal suppression. Nichols, Nugent, and Tyler (1965) have demonstrated virtually complete suppression of the secretion of cortisol by the adrenal gland for a period of 24 hours following the administration of a physiological dose of corticosteroid (0.5 mg. dexamethasone) given at midnight. The same amount given at 8 a.m. or 4 p.m. caused only temporary suppression of cortisol secretion.

In the present study we have compared the effect of two regimens of corticosteroid administration on

HPA axis suppression as measured by the diurnal rhythm of plasma 11-OHCS and the plasma 11-OHCS response to β^{1-24} tetraacosapeptide (Synacthen CIBA), lysine⁸-vasopressin, and insulin-induced hypoglycaemia. The two regimens were: a 4 mg. oral dose of Triamcinolone given at 10 p.m. every day and an 8 mg. oral dose of Triamcinolone given at 8 a.m. every alternate morning. Two groups of patients were treated contemporaneously with one or other of these regimens for a period of exactly one year.

Material and Methods

Patients Studied

Twelve patients with "definite" or "classical" rheumatoid arthritis were studied. All had active polyarthritis of at least 6 months' duration, associated with a positive sheep cell agglutination test (SCAT) and radiological evidence of articular erosions in the hands and feet, or both. Definite indication for oral corticosteroid therapy was present in each patient studied: aspirin, phenylbutazone, and indomethacin when given in full doses, singly or in combination, had failed to control the joint symptoms adequately. The patients were admitted to the study consecutively, but divided randomly into two equal groups of six. Their salient clinical and laboratory findings are summarized in Table I (opposite), which shows that they were fairly comparable with respect to duration and severity of their joint disease. To one group Triamcinolone was given orally in a dose of 8.0 mg. every 48 hours at 8 a.m., and the other group received Triamcinolone orally in a dose of 4.0 mg. daily given at 10 p.m.

Tests of HPA Axis

The following procedures were employed to assess HPA axis function before starting therapy and at the end

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TABLE I
SUMMARY OF SALIENT CLINICAL AND LABORATORY FINDINGS IN TWELVE PATIENTS WITH
RHEUMATOID ARTHRITIS

Patient No.	Age (yrs)	Sex	Duration of Arthritis (yrs)	Subcutaneous Nodules	Articular Index*	Hb. (g./100 ml.)	ESR (Westergren) (mm./hr)	SCAT	Serum		X-ray Stage of Arthritis†
									Albumin (g./100 ml.)	Globulin (g./100 ml.)	
1	47	M	0.75	—	24	14.8	45	1:128	3.0	3.4	I
2	41	F	1.0	+	20	11.2	27	1:128	3.2	3.6	III
3	45	F	1.5	+	31	14.6	25	1:64	3.7	2.9	I
4	36	F	2.0	—	18	14.0	28	1:64	3.3	2.7	III
5	46	F	1.0	—	34	11.3	30	1:64	3.8	2.8	I
6	40	F	10.0	—	34	12.5	35	1:128	3.3	3.0	III
Mean Range	42.5 (36—47)		2.7 (0.75—10)		26.8 (18—34)	13.1 (11.3—14.8)	31.7 (25—45)		3.4 (3.0—3.8)	3.1 (2.7—3.6)	
7	48	F	3.0	+	27	11.9	23	1:128	3.6	3.4	III
8	44	M	1.0	—	23	12.2	54	1:128	3.1	3.8	III
9	43	F	3.0	+	49	10.0	45	1:128	2.3	4.4	III
10	47	F	2.0	—	17	11.8	31	1:64	3.5	2.3	I
11	45	F	8.0	—	15	12.5	67	1:256	3.9	3.6	III
12	44	F	0.5	+	18	13.2	42	1:512	2.8	3.8	I
Mean Range	45.2 (43—48)		2.9 (0.5—8.0)		24.8 (15—49)	11.9 (10.0—13.2)	43.6 (23—67)		3.2 (2.3—3.9)	3.6 (2.3—4.4)	

*Articular Index is used as a clinical assessment of the state of joint involvement. It is based on the pain felt by the patient after firm pressure on each joint. The pain response is graded 0 (no pain); +1 (slightly tender), +2 (moderately tender), and +3 (severely tender). The score for each individual joint are summed to give the articular index (Jasani and others, 1967).

†Classification of Steinbrocker, Traeger, and Batterman (1949).

of one year's treatment. All tests were carried out during in-patient stay. Patients were admitted for 4 days before any test procedure was carried out.

Diurnal Variation of Plasma 11-OHCS

The diurnal variation of plasma 11-OHCS was determined at 8 a.m. and 10 p.m. All patients rested in bed for at least 30 minutes before the venepuncture. At the end of one year's treatment, diurnal variation was determined without stopping Triamcinolone. In this study diurnal rhythm of plasma 11-OHCS has been expressed in the manner described by Perkoff, Eik-Nes, Nugent, Fred, Nimer, Rush, Samuels, and Tyler (1959).

Synacthen Test

The Synacthen (β^{1-24} tetraacosapeptide, CIBA) test was carried out, as previously described from this centre (Grieg, Boyle, Jasani, and Maxwell, 1967), at 9 a.m. with the patients resting in bed having had a light breakfast.

Lysine⁸-Vasopressin Test

The lysine⁸-vasopressin test was performed as described by Gwinup (1965). Basal plasma 11-OHCS was determined at 9 a.m. after a light breakfast. Lysine⁸-vasopressin in a dose of 10 pressor units was injected intramuscularly (gluteal region). The rise in plasma 11-OHCS was determined at 60 and 120 minutes after the injection.

Insulin-induced Hypoglycaemia Test

This test was carried out using the standard procedure of Landon, Wynn, and James (1963). All patients in the present study received 0.15 u./kg. body wt. dose of soluble insulin given intravenously. Two basal plasma 11-OHCS levels were determined at an interval of 30 minutes. Further venous blood samples to detect the rise in plasma 11-OHCS were taken at 30, 60, 90, and 120 minutes after administration of soluble insulin. Blood sugars were also determined at the same time intervals using a standard ferro ferricyanide method with an Auto-Analyzer (Technicon).

Criteria of Normal Response

The normal range of response (mean $\pm$ 2 S.D.) for the synacthen and insulin-induced hypoglycaemia tests in our hands have already been reported (Jasani and others, 1967). Our range of normal response (mean $\pm$ 2 S.D.) to intramuscular administration of lysine⁸-vasopressin is similar to our range for intravenous lysine⁸-vasopressin (Jasani and others, 1967).

Plasma 11-OHCS were assayed by the method of Mattingly (1962). The fluorescence obtained with use of the sulphuric acid-ethanol reagent in this method is largely due to cortisol, but also includes small amounts due to corticosterone (Mattingly, 1962). Triamcinolone is known not to influence the results of this assay procedure (Mattingly, 1962) to any significant degree.

Results

The results are summarized in Tables II and III.

Diurnal Rhythm of Plasma 11-OHCS

Table II shows the individual plasma 11-OHCS levels obtained at 8 a.m. and 10 p.m. in the two groups of patients before administration of Triamcinolone and after one year's therapy.

The mean daily decrement in plasma 11-OHCS before starting steroid therapy was $-9\mu\text{g./100 ml.}$ (Table II) in the group given Triamcinolone on alternate mornings, and in the group given a daily evening dose of Triamcinolone the mean plasma 11-OHCS decrement was $-8.8\mu\text{g./100 ml.}$ (Table

II). The corresponding values at the end of one year's therapy were 8.9 and $-0.5\mu\text{g./100 ml.}$ respectively. This difference between the two groups of patients was not statistically significant before starting steroid therapy, but was highly significant by a Student's "t" test ($P < 0.001$) at the end of one year's therapy. Using our criteria of normal diurnal variation of plasma 11-OHCS (range -3 to $-15\mu\text{g./100 ml.}$, $-9\mu\text{g./100 ml.}$), every patient given a daily evening dose of Triamcinolone exhibited complete loss of diurnal variation of plasma 11-OHCS at the end of one year's therapy (Table II). In contrast, none of the patients receiving 8 mg. Triamcinolone on alternate mornings showed abnormality of plasma 11-OHCS diurnal

TABLE II
DIURNAL VARIATION OF PLASMA 11-OHCS ($\mu\text{g. per 100 ml.}$) IN TWO GROUPS OF PATIENTS

Dosage of Triamcinolone		Before Treatment			After Treatment		
		8 a.m.	10 p.m.	Decrement* ($\mu\text{g./100 ml.}$)	8 a.m.	10 p.m.	Decrement* ($\mu\text{g./100 ml.}$)
8 mg. every alternate morning	1	19.5	12.0	-7.5	17.0	8.5	-9.5
	2	13.5	4.0	-9.5	18.0	7.5	-11.5
	3	21.0	6.0	-15.0	11.0	3.0	-8.0
	4	19.0	10.8	-8.2	15.0	7.5	-7.5
	5	16.0	8.5	-7.5	14.5	5.0	-9.5
	6	11.0	4.0	-7.0	15.0	7.5	-7.5
	Mean $\pm$ S.D. $\pm$ S.E.			-9.1 -3.6 ± 1.2			-8.9 -1.6 ± 0.6
4 mg. every night	7	12.0	7.5	-4.5	5.0	4.5	-0.5
	8	14.3	7.5	-6.8	6.0	6.5	+0.5
	9	13.3	7.0	-6.3	8.0	7.0	-1.0
	10	18.5	5.5	-13.0	4.0	3.0	-1.0
	11	16.5	4.5	-12.0	4.5	4.0	-0.5
	12	15.0	5.0	-10.0	6.0	5.5	-0.5
	Mean $\pm$ S.D. $\pm$ S.E.			-8.8 -3.4 ± 1.4			-0.5 -0.5 ± 0.2

*The 8 a.m. level of plasma 11-OHCS is taken as zero, and the difference between 8 a.m. and 10 p.m. levels is expressed as the decrement (using the convention of Perkoff and others, 1959).

TABLE III
PLASMA 11-OHCS RESPONSE TO HPA AXIS TESTS IN TWO GROUPS OF PATIENTS

Tests of HPA Axis				Synacthen Test		Lysine*-Vasopressin Test		
				0 min.	30 min.	0 min.	60 min.	120 min.
Dosage of Triamcinolone	8 mg. every alternate morning (Patients 1-6)	Before	Mean	14.6	35.0	15.5	38.0	22.7
			±S.D.	±5.3	±7.4	±4.3	±7.2	±6.6
			±S.E.	±2.2	±3.0	±1.8	±2.9	±1.7
		After	Mean	17.4	31.8	13.2	31.8	25.5
			±S.D.	±4.2	±5.7	±3.1	±7.6	±1.1
			±S.E.	±1.7	±2.3	±1.3	±3.1	±0.3
	4 mg. every night (Patients 7-12)	NS*			NS	NS	NS	NS
		Before	Mean	18.7	33.8	18.0	38.4	23.3
			±S.D.	±3.4	±6.8	±4.6	±5.7	±7.7
			±S.E.	±1.4	±2.8	±1.9	±2.3	±1.9
		After	Mean	10.3	28.5	11.5	33.8	21.1
			±S.D.	±3.0	±8.4	±3.0	±5.3	±7.7
			±S.E.	±1.2	±3.4	±1.2	±2.2	±0.0
			P<0.01	NS	P<0.02	NS		

*NS=not significant by Student's "t" test.

rhythm. Applying Fisher's exact test for 2×2 tables (Bailey, 1959) to these results, the difference in proportions observed is significant at the 1 per cent. level.

Synacthen Test

The results of plasma 11-OHCS response to Synacthen before and after therapy for each group of patients are shown in Table III. Before starting steroid therapy there was no significant difference between the mean resting value of plasma 11-OHCS and the mean levels attained 30 minutes after 0.25 mg. Synacthen in the two groups of patients studied.

After one year's therapy, the mean resting plasma 11-OHCS concentration was $10.3 \mu\text{g./100 ml.}$ ($\pm$ S.E. $1.2 \mu\text{g./100 ml.}$) in the group of patients given a daily evening dose of Triamcinolone. This value is significantly lower than the corresponding figure of $18.7 \pm 1.8 \mu\text{g./100 ml.}$ observed in this group before steroid therapy. In the group of patients who received Triamcinolone on alternate mornings, no significant difference was observed in the mean plasma 11-OHCS level before and after one year's steroid therapy (14.6 ± 2.2 and $17.4 \pm 1.7 \mu\text{g./100 ml.}$ respectively). The response to synacthen stimulation was normal in both groups of patients before and after steroid therapy (Table III).

Lysine⁸-Vasopressin Test

Values of plasma 11-OHCS observed during the response to lysine⁸-vasopressin stimulation in the two groups of patients studied are shown in Table III.

Before administration of Triamcinolone the mean resting plasma 11-OHCS concentrations were similar

in the two groups of patients (Table III), and the levels obtained at 60 and 120 minutes with 10 pressor units of lysine⁸-vasopressin administered intramuscularly were virtually identical (Table III).

At the end of one year's therapy the mean plasma 11-OHCS values at 0, 60, and 120 minutes during this test in the group receiving 8 mg. Triamcinolone on alternate mornings were: 13.2 ± 1.3 , 31.8 ± 3.1 , and $21.5 \pm 3.3 \mu\text{g./100 ml.}$ The corresponding levels for the group of patients given a daily evening dose of 4.0 mg. Triamcinolone were 11.5 ± 1.2 , 33.8 ± 2.2 , and $22.1 \pm 4.0 \mu\text{g./100 ml.}$ This group of patients again had a low starting mean plasma 11-OHCS value in the morning which was significantly different from the mean morning value before Triamcinolone was administered. Both groups of patients demonstrated a normal response to lysine⁸-vasopressin stimulation.

Insulin-induced Hypoglycaemia Test

The responses of both groups to insulin hypoglycaemia before therapy are shown in Table III, which also shows a comparison of the results before and after one year's steroid therapy in each group. Both groups had normal (and similar) responses to hypoglycaemia before Triamcinolone therapy. After one year's treatment with Triamcinolone, each patient in the group who had received the alternate morning schedule of administration still had normal plasma 11-OHCS responses to insulin hypoglycaemia although the mean values at 60 and 120 minutes for the group as a whole were significantly lower than the corresponding values before steroid therapy. (Before steroid therapy the mean plasma 11-OHCS values at -30, 0, 30, 60, 90, and 120 minutes were 17.6 ± 1.8 , 14.5 ± 1.7 , 18.0 ± 1.5 , 35.2 ± 1.4 , 39.8

II
BEFORE AND AFTER TREATMENT WITH TRIAMCINOLONE FOR ONE YEAR

Insulin Hypoglycaemia Test					
-30 min.	0 min.	30 min.	60 min.	90 min.	120 min.
17.6 ± 4.5 ± 1.8	14.5 ± 4.2 ± 1.7	18.0 ± 3.7 ± 1.5	35.2 ± 3.3 ± 1.4	39.8 ± 6.5 ± 2.6	34.0 ± 3.3 ± 1.4
14.6 ± 2.4 ± 1.0	14.7 ± 6.6 ± 2.0	15.7 ± 5.5 ± 2.2	29.3 ± 5.7 ± 2.3	33.0 ± 4.6 ± 1.9	28.5 ± 3.6 ± 1.5
NS	NS	NS	$P < 0.05$	$P < 0.1 > 0.05$	$P < 0.02$
16.4 ± 3.6 ± 1.5	15.0 ± 4.2 ± 1.7	18.7 ± 6.3 ± 2.6	36.0 ± 5.7 ± 2.3	39.7 ± 4.0 ± 1.6	33.4 ± 9.7 ± 3.9
12.2 ± 3.2 ± 1.3	10.3 ± 3.6 ± 1.5	12.9 ± 6.3 ± 2.6	22.2 ± 3.1 ± 1.3	22.7 ± 3.9 ± 1.6	18.2 ± 3.8 ± 1.5
NS	NS	NS	$P < 0.001$	$P < 0.001$	$P < 0.01$

± 2.6 , and 34.0 ± 1.4 $\mu\text{g./100 ml.}$; after steroid therapy these figures were 14.6 ± 1.0 , 14.7 ± 2.0 , 15.7 ± 2.2 , 29.3 ± 3.0 , 33.0 ± 1.9 , and 28.5 ± 1.5 $\mu\text{g./100 ml.}$ respectively.

After one year's treatment with Triamcinolone two of the six patients who had received the daily evening dose regimen demonstrated a slightly subnormal plasma 11-OHCS response to insulin hypoglycaemia, and the mean plasma 11-OHCS values for the group were highly significantly lower at 60, 90, and 120 minutes after insulin (Before steroid therapy the mean plasma 11-OHCS values were 16.4 ± 1.5 , 15.0 ± 1.7 , 18.7 ± 2.6 , 36.0 ± 2.3 , 39.7 ± 1.6 , and 33.4 ± 3.9 $\mu\text{g./100 ml.}$; after steroid therapy the corresponding values were: 12.2 ± 1.3 , 10.3 ± 1.5 , 12.9 ± 2.6 , 22.2 ± 1.3 , 22.7 ± 1.6 , and 18.2 ± 1.5 $\mu\text{g./100 ml.}$ respectively).

These data suggest that patients who received the daily evening regimen of steroid administration have a more subnormal response to insulin hypoglycaemia compared with patients who were treated with the regimen of steroid administration on alternate mornings. This suggestion is strengthened by the observation that the mean 11-OHCS response to insulin was significantly lower at 90 and 120 minutes in the patients receiving the evening schedule compared with patients receiving the alternate morning schedule (Table III).

Discussion

This study was designed to assess the influence of two different regimens of administration of oral corticosteroid drugs on HPA axis suppression. The reasons for selection of these regimens were as follows:

(1) Harter and others (1962) suggested alternate daily single-dose corticosteroid therapy on the grounds that less adrenal suppression was thereby produced than with multiple daily doses.

(2) Nichols and others (1965) showed that a small single dose of dexamethasone given at midnight resulted in virtually complete suppression of plasma 17-OHCS levels and of cortisol secretion by the adrenal gland for 24 hours, resulting in loss of diurnal variation in plasma cortisol; they suggested that it might be possible to avoid adrenal suppression by omitting the nightly dose of corticosteroid.

However, some workers (De Andrade, McCormick, and Hill, 1964) have shown that the small nightly dose of corticosteroid results in more adequate symptom relief in some patients with rheumatoid arthritis. It seemed important to determine the

relative HPA axis suppressive effects of these regimens on a long-term basis.

The results show that patients given a daily evening dose of Triamcinolone developed complete loss of diurnal rhythm of plasma 11-OHCS and this observation is in accord with the findings of Nichols and others (1965). When patients were treated with 8 mg. Triamcinolone on alternate mornings, however, no abnormality of diurnal rhythm was apparent even after one year of treatment. This observation suggests that the integrity of diurnal rhythm during this regimen of steroid administration may remain permanently unaltered. This finding does not necessarily imply long-term integrity of the HPA axis.

At the end of one year's therapy both groups of patients had responses to insulin-induced hypoglycaemia which were significantly poorer compared with their responses before therapy. This observation suggests that HPA axis suppression may be induced by both of these regimens of corticosteroid administration on a long-term basis. Admittedly the degree of suppression observed in the present study was slight because the responses of both groups of patients to Synacthen and to lysine⁸-vasopressin were normal. However, one might expect that longer administration of corticosteroid, perhaps in higher dosage, might produce more marked suppression of the axis resulting in abnormalities of the plasma 11-OHCS responses to Synacthen and to lysine⁸-vasopressin.

Significantly greater impairment of the plasma 11-OHCS response to insulin hypoglycaemia stimulation was present in the group of patients given a single daily evening dose of corticosteroid.

The finding of low morning plasma 11-OHCS levels in the group of patients given daily evening Triamcinolone therapy reflects the suppression of cortisol production for 24 hours which was described by Nichols and others (1965) after a physiological dose of steroid given at midnight. From the practical point of view the adrenal glands of these patients can still respond to Synacthen stimulation and they are able to respond to lysine⁸-vasopressin stimulation in spite of the fact that they have presumably had reduction of ACTH release from the pituitary gland and of cortisol from the adrenal glands for one year. Nonetheless, these patients do show more significant suppression of the HPA axis as judged by their capacity to elevate plasma 11-OHCS levels in response to insulin-induced hypoglycaemia than do the patients given the regimen of 48-hour single-dose treatment advocated by Harter and others (1965). It would appear that the latter regimen causes less HPA

axis suppression when corticosteroid drugs are given in PHYSIOLOGICAL amounts, and this finding parallels the observation of Harter and others (1965) that less adrenal suppression results from this regimen when corticosteroids are given in PHARMACOLOGICAL amounts.

Data has previously been presented in a retrospective study which suggests that an impaired plasma 11-OHCS response to insulin-induced hypoglycaemia is likely to be the first abnormality to develop in corticosteroid-induced HPA axis suppression (Jasani and others, 1967). The present prospective study confirms this suggestion.

A consideration of the clinical progress of both groups of patients is appropriate: to show that less significant suppression of the HPA axis occurs with one regimen of therapy is of little value unless it can be demonstrated that the symptomatic benefit achieved by this regimen is equipotent with other schemes of corticosteroid dosage. As can be seen from Table IV, there was a comparable fall in the articular index in both groups of patients after one year of corticosteroid therapy. This objective evaluation of analgesic response was not, however, confirmed by symptom inquiry. The patients

receiving 4 mg. Triamcinolone nightly at 10 p.m. experienced mild pain and tiredness around 6 p.m. on the following evening. Two of the patients receiving Triamcinolone 8 mg. every alternate morning complained of mild pain on the morning before their next dose. It is obvious that more observations on more patients require to be made before one can propose with confidence that the single dose of Triamcinolone given on alternate mornings is preferable to the single daily evening dose.

Summary

A prospective study of the degree of suppression of the hypothalamo-pituitary-adrenal (HPA) axis after two regimens of oral corticosteroid therapy has been undertaken in twelve patients with rheumatoid arthritis. Diurnal rhythm of plasma 11-OHCS and the plasma 11-OHCS response to synacthen, lysine⁸-vasopressin, and insulin hypoglycaemia stimulation was studied before and after one year's treatment with Triamcinolone. Six patients received a single daily evening dose of 4 mg.; six patients were given a single dose of 8 mg. on alternate mornings.

Slight but significant HPA axis suppression was seen with both regimens of steroid administration, as manifested by diminished plasma 11-OHCS responses to insulin induced hypoglycaemia. This response was significantly more impaired in the patients who had received Triamcinolone in a single evening dose than in those who had received the corticosteroid on alternate mornings. Diurnal rhythm was unaltered in the latter patients after one year's treatment with Triamcinolone but was uniformly abolished in the former patients. The data confirm in a prospective fashion the suggestion that the plasma 11-OHCS response to insulin hypoglycaemia is the first to become impaired during long-term corticosteroid therapy.

Neither group of patients derived total symptom relief from either regimen of therapy. More observations are required to assess fully the clinical value of alternate morning therapy.

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TABLE IV
ARTICULAR INDICES IN TWO GROUPS OF PATIENTS
GIVEN DIFFERENT REGIMENS OF TRIAMCINOLONE
FOR ONE YEAR

Dosage of Triamcinolone		Articular Index	
		Before Corticosteroid Administration	After Corticosteroid Administration
8 mg. every alternate morning	1	24	6
	2	20	8
	3	31	6
	4	18	3
	5	34	8
	6	34	8
	Mean ±S.D. ±S.E.	26.8 ±7.1 ±2.9	6.5 ±2.0 ±0.8
4 mg. every night	7	27	6
	8	23	6
	9	49	18
	10	17	2
	11	15	2
	12	18	2
	Mean ±S.D. ±S.E.	24.8 ±12.6 ±5.1	6.0 ±6.2 ±2.5

Using a Student's "t" test, no significant difference was noted in the articular index between the group of patients receiving 8 mg. triamcinolone every 48 hours (8 a.m.) and the group receiving 4 mg. triamcinolone daily (10 p.m.) at the end of one year's treatment.

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L'inhibition de l'axe hypothalamo-pituitaire-adrenal au cours de deux régimes de thérapie corticostéroïdienne

RÉSUMÉ

On étudia l'intensité de l'inhibition de l'axe hypothalamo-pituitaire-adrenal (HPA) après deux régimes de thérapie corticostéroïdienne par voie orale chez douze malades atteints de polyarthrite rhumatoïde. On détermina le rythme diurne des 11-hydroxycorticostéroïdes plasmatiques et leur réponse au Synacthen, à la lysine⁸-vasopressine et à l'hypoglycémie induite par l'insuline avant et après une année de traitement par la triamcinolone. Six malades suivaient un régime d'une seule dose de 4 mg. tous les soirs et six autres recevaient une seule dose de 8 mg. tous les deux matins.

Inhibición del eje hipotálamo-pituitario-adrenal en el curso de dos regímenes de tratamiento corticosteroideo

SUMARIO

Se estudió la intensidad de la inhibición del eje hipotálamo-pituitario-adrenal (HPA) después de dos regímenes de terapia corticosteroidea por vía oral en doce enfermos con poliartritis reumatoide. Se determinaron el ritmo diurno de los 11-hidroxycorticosteroides plasmáticos y su respuesta al Synacthen, a la lisina⁸-vasopresina y a la hipoglicemia inducida por la insulina, antes y después de un año de tratamiento con la triamcinolona. Seis enfermos fueron sometidos a una sola dosis vespéral de 4 mg. de triamcinolona y seis otros a una sola dosis matutina cada dos días de 8 mg. de triamcinolona.

Une inhibition légère mais significative de l'axe HPA fut observée avec les deux régimes de thérapie stéroïdienne, se traduisant par des réponses affaiblies des 11-hydroxycorticostéroïdes plasmatiques à l'hypoglycémie induite par l'insuline. Cette réponse fut significativement plus faible chez les malades recevant la dose vespérale que chez ceux qui prenaient leur triamcinolone tous les deux matins. Le rythme diurne ne changea pas chez ceux-ci après un an de traitement, mais il fut uniformément aboli chez les malades au régime vespéral. Ces résultats confirment l'hypothèse selon laquelle la réponse des 11-hydroxycorticostéroïdes plasmatiques à l'hypoglycémie insulinaire s'affaiblit le premier lors d'une thérapie corticostéroïde prolongée.

Ni l'un ni l'autre groupe de malades n'obtint un soulagement total au cours de ces régimes thérapeutiques. Une observation plus longue est nécessaire pour bien évaluer les avantages du dosage tous les deux jours.

Una inhibición ligera pero significativa del eje HPA se observó con ambos regímenes esteroideos, manifestándose por respuestas débiles de los 11-hidroxycorticosteroides a la hipoglicemia insulínica. Esta respuesta fue significativamente más floja en los que recibían la dosis vespéral que en los que recibían la triamcinolona por la mañana cada dos días. Después de un año de tratamiento el ritmo diurno fue sin cambiar en los últimos, pero se vió uniformemente abolido en los primeros. Estos resultados confirman la hipótesis de que la respuesta de los 11-hidroxycorticosteroides plasmáticos a la hipoglicemia insulínica se debilita primera en el curso de una terapia corticosteroidea sostenida.

En ninguno de los grupos los enfermos beneficiaron de un alivio completo. Se necesita más tiempo de observación para apreciar las ventajas clínicas del tratamiento cada dos días.