

Effect of alternate-day steroid administration on adrenal function in allergic children

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Twenty-four allergic children were given equivalent high and low doses of dexamethasone and prednisone on an alternate-day schedule, and adrenal function was determined by adrenocorticotrophic hormone (ACTH) response tests before and at the end of each treatment period. Adrenal suppression was not demonstrated in prednisone-treated patients but did occur in those taking the larger dose of dexamethasone. Adrenal response tests with synthetic ACTH were done in another group of 24 asthmatic children who had required alternate-day prednisone for periods of 6 to 42 months. Only one patient of the group had impaired adrenal responsiveness. It is concluded that, in equivalent doses, prednisone has less adrenal suppressive activity than does dexamethasone and that long-term alternate-day prednisone administration in the doses used does not ordinarily produce an impaired adrenal response to exogenous ACTH.

Although the long-term use of corticosteroids is necessary to enable a small number of severely asthmatic children to participate in day-to-day activity, adrenal suppression may be a serious, even fatal, complication of such treatment. The concept of intermittent therapy to control the adverse effects of corticosteroids was first introduced by Lange and associates^{1, 2} in 1958 for the treatment of nephrosis, using a schedule of 3 days of steroid treatment followed by 4 days without treatment to allow for adrenal recovery. It was subsequently shown by Siegel and associates³ that asthmatic children treated in this manner still had some adrenal suppression at the end of the 4 nonsteroid days.

In 1963 Harter and co-workers⁴ introduced the concept of alternate-day treatment using prednisone. They found no indication of adrenal suppression as evidenced by urinary steroid excretion or adrenal response to adrenocorticotrophic hormone (ACTH) injection in adult asthmatic patients. Others⁵⁻⁷ have reported that the therapeutic effects achieved with alternate-day corticosteroid treatment of asthmatic patients are accompanied by less adrenal suppression

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than that produced by daily treatment. In general, relatively short-acting corticosteroids, such as prednisone, are thought to afford the best results, because the adrenal gland is able to recover when treatment is interrupted.

The purpose of this article is to report on three related investigative studies of adrenal function in asthmatic children, two evaluating alternate-day steroid treatment and one evaluating the use of synthetic ACTH in determining adrenal activity.

STUDY NO. 1

The first study was done to compare the adrenal suppressive activity of prednisone with that of a newer synthetic compound—dexamethasone—in equivalent anti-inflammatory doses^{6, 12} administered on alternate days. Previous reports⁶ suggested that different corticosteroids have varying effects on the adrenal glands during alternate-day therapy. To assess the effects of these two drugs, 24 allergic children, 5 to 16 years of age, who required corticosteroid treatment were studied. They had received little, if any, previous corticosteroid therapy—none within the previous 6 months.

Patients were divided into four comparable groups and treated with alternate-day steroids for two consecutive 3 week periods. Half of the 24 children were treated with prednisone and half with dexamethasone. Children in one group were initially given either high doses (30 mg. of prednisone or 4.5 mg. of dexamethasone) or low doses (10 mg. of prednisone or 1.5 mg. of dexamethasone) during the first 3 week treatment period. Each group was switched to the opposite dose of the same drug during the second 3 week period.

Adrenal responsiveness was estimated by comparing the serum concentration of 11-hydroxy-corticosteroids (11-OHCS) before and 2 hours after the intramuscular injection of 25 units of ACTH. The ACTH response tests were performed at the same time of day before treatment and at the end of each 3 week treatment period, on a day when the patient did not receive corticosteroids. Control data were obtained from 8 nonsteroid-treated asthmatic children on whom serum 11-OHCS levels were determined before and 2 hours after intramuscular injection of ACTH or saline and from 6 normal volunteers given ACTH.

Test method

No corticosteroids were given on the day of the ACTH response test. At 9:00 A.M., 12 ml. of blood were drawn into a syringe rinsed with heparin. The patient was then given 25 units of ACTH (1.25 ml.) intramuscularly, and 2 hours later a second 12 ml. blood specimen was drawn. All specimens were spun 15 minutes at 2,000 to 3,000 r.p.m., and the plasma was transferred to small tubes and frozen. Serum concentrations of 11-OHCS were determined by a modification of the fluorescent method of Mattingly.^{8, 13, 14}

Results

The control data are shown in Table I. The experimental data were challenged by analysis of covariance. Comparison of posttreatment responses to ACTH with pretreatment control values indicated that treatment with prednisone did not

TABLE I. 11-OHCS responses in normal and nonsteroid-treated asthmatic children

Time	Mean plasma 11-OHCS levels (μ g %)		
	Normal children (ACTH)	Asthmatic children	
		ACTH	Saline
Before injection	6.5	5.1	4.9
2 Hours after injection	16.9	16.1	5.4
Increase	10.4	11.0	0.5

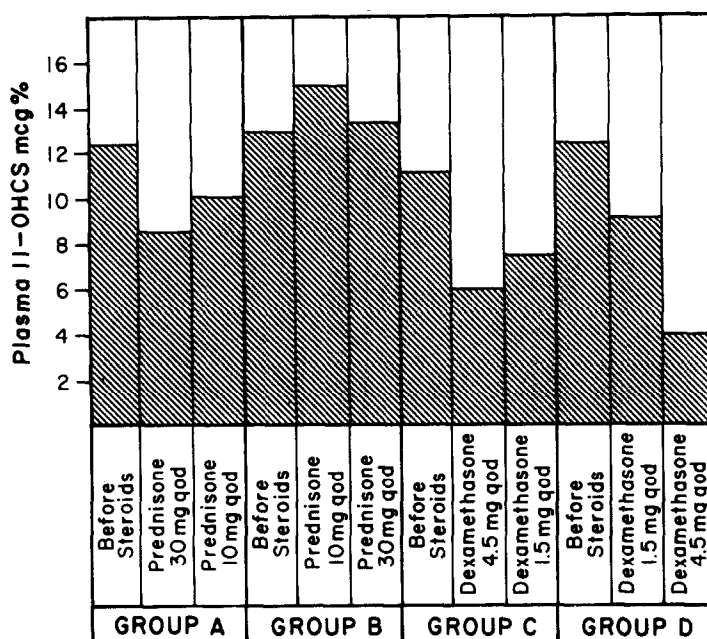


FIG. 1. Adrenal response to ACTH in allergic children treated with alternate-day prednisone and dexamethasone (mean plasma 11-OHCS μ g per cent).

TABLE II. ACTH response in allergic children taking alternate-day prednisone and dexamethasone

Patient groups	Plasma 11-OHCS (mcg %)								
	Control			First treatment period			Second treatment period		
	Before ACTH	After ACTH	Mean rise	Before ACTH	After ACTH	Mean rise	Before ACTH	After ACTH	Mean rise
Group A									
Pred. 30 mg. q.o.d. 1st period	5.3	18.5	12.4	4.6	13.2	8.6	5.2	15.4	10.0
Pred. 10 mg. q.o.d. 2nd period	± 1.4	± 5.2		± 5.4	± 6.4		± 2.0	± 4.4	
Group B									
Pred. 10 mg. q.o.d. 1st period	5.4	18.4	13.0	5.7	20.8	15.0	5.2	18.6	13.4
Pred. 30 mg. q.o.d. 2nd period	± 1.9	± 2.6		± 2.5	± 6.3		± 2.0	± 3.5	
Group C									
Dexa. 4.5 mg. q.o.d. 1st period	5.7	16.8	11.2	3.1	9.1	6.0*	3.8	11.3	7.5
Dexa. 1.5 mg. q.o.d. 2nd period	± 1.9	± 1.8		± 1.1	± 2.3		± 1.7	± 5.3	
Group D									
Dexa. 1.5 mg. q.o.d. 1st period	5.4	17.1	12.5	4.6	13.3	8.7	4.9	8.9	4.0*
Dexa. 4.5 mg. q.o.d. 2nd period	± 1.7	± 5.8		± 2.1	± 1.8		± 4.0	± 2.1	

Pred. = prednisone; q.o.d. = every other day; Dexa. = dexamethasone.

* $p < .01$.

produce significant adrenal suppression at any dose or sequence of administration, whereas treatment with high doses of dexamethasone resulted in highly significant suppression in any sequence of treatment (Table II and Fig. 1). These results indicate that alternate-day treatment with prednisone does not produce adrenal suppression at the doses and for the duration of treatment studied,

TABLE III. Adrenal response to natural and synthetic ACTH in 20 asthmatic children

No. patients	Mean plasma 11-OHCS levels ($\mu\text{g } \%$)					
	Synthetic ACTH			Natural ACTH		
	Before	After	Increase	Before	After	Increase
6 (Cortrosyn first)	6.4	17.4*	11.0	5.4	14.8†	9.5
6 (ACTH first)	6.0	16.3*	10.3	5.3	16.2†	10.9
8 (Prior ACTH test)	5.4	16.1*	10.7	5.9	16.8†	10.9
20 Total	5.9	16.5*	10.6	5.6	16.1†	10.5

*At one hour.

†At 2 hours.

whereas 4.5 mg. of dexamethasone given in the same manner significantly depressed adrenal activity.

STUDY NO. 2

This study was done only to confirm that adrenal stimulation one hour after injection of synthetic ACTH (Cortrosyn)* is equivalent to that occurring 2 hours after injection of natural ACTH.† Available data suggest that this synthetic polypeptide, containing the first 24 amino acids in sequence from the N terminal found in ACTH, stimulates the adrenal cortex more rapidly than does the natural product and is considerably less antigenic.⁹⁻¹¹

Twenty children with asthma, aged 8 to 15 years and of both sexes, were selected because they had received neither extensive nor recent corticosteroid therapy. Eight had undergone ACTH response tests previously. Twelve others underwent response tests with the use of both substances at 2 week intervals, 6 receiving the synthetic ACTH and 6 the natural ACTH first. At 9:00 A.M. on the test day after a base-line venous blood specimen was obtained, 0.25 mg. of the synthetic or 25 units of the natural ACTH was injected intramuscularly. A second blood specimen was drawn one hour after injection of the synthetic and 2 hours after the natural ACTH. Mean plasma 11-OHCS concentrations were determined by the same modification of Mattlingly's fluorescent method referred to earlier.

Results

There were no significant differences in adrenal responsiveness one hour after the administration of the synthetic compared to 2 hours after natural ACTH (Table III). No hypersensitivity reactions occurred. The test with the synthetic agent obviously requires less time to complete and significantly diminishes the possibility of hypersensitivity reactions to ACTH.

STUDY NO. 3

This study was done as a continuation of Harter and associates'⁴ original work and the first part of this study demonstrating the lack of adrenal suppression after short periods of treatment with prednisone in asthmatic children.

Twenty-four asthmatic children, aged 2 to 19 years who had been treated with prednisone on alternate days for 6 to 42 months, were evaluated for adrenal responsiveness. Their average alternate-day doses ranged from 7.5 mg. to 20 mg., and all patients had been managed with occasional short courses of daily steroids during acute asthmatic exacerbations or other periods of stress. Adrenal responsiveness was determined by measurement of the rise in plasma 11-OHCS (measured by fluorometry) one hour after intramuscular administration of 0.25 mg. of synthetic ACTH.

*Cortrosyn for this study kindly supplied by Organon Inc., West Orange, N. J.

†ACTHAR, Armour Pharmaceutical Company, Chicago, Ill.

TABLE IV. Adrenal response to synthetic ACTH in asthmatic children treated with long-term alternate-day prednisone: Effect of duration of therapy

Months of alternate-day treatment	No. patients	Mean age	Mean rise in 11-OHCS ($\mu\text{g}\%$)
<12*	7*	9.5*	9.3*
12-24	8	9.2	12.6
25-36	5	8.6	11.8
>36	4	14.0	11.0

*One patient with adrenal suppression in this group.

TABLE V. Adrenal response to synthetic ACTH in asthmatic children treated with long-term alternate-day prednisone: Effect of dose

Mean alternate-day dose prednisone (mg.)	No. patients	Mean age	Mean rise 11-OHCS ($\mu\text{g}\%$)
7.5	5	8.2	12.5
10	5	8.6	11.2
12.5	7	11.5	11.0
15*	5*	10.0*	10.0*
20	2	10.0	10.5

*One patient with adrenal suppression in this group.

TABLE VI. Adrenal response to synthetic ACTH in asthmatic children treated with long-term alternate-day prednisone: Effect of total therapy

Total treatment (mg. $\times$ mo.)	No. patients	11-OHCS ($\mu\text{g}\%$)		
		Before ACTH	After ACTH	Rise
<100	3	5.2	16.3	11.1
100-200*	10*	9.2*	20.4*	11.2*
200-300	2	6.2	17.8	11.6
300-400	3	6.7	17.2	10.5
400-500	3	4.6	15.7	11.0
>500	3	3.8	15.1	11.3

*One patient with adrenal suppression in this group.

Results

Only one patient of the 24, an 11-year-old girl taking an average of 15 mg. of prednisone on alternate days for just less than one year, had adrenal suppression. In all other patients the adrenal response was within the normal range of values (Tables IV, V, and VI).

Our findings indicate that long-term, alternate-day prednisone therapy of asthmatic children in the dose range described will not ordinarily induce significant adrenal suppression as measured by the ACTH response test. Since the one patient who did show suppressed adrenal activity was in neither the largest dose nor the longest duration of treatment group, the possibility of an unusual individual sensitivity to the pituitary-adrenal suppressive activity by corticosteroids is suggested.

COMMENTS

These studies are not meant to imply that alternate-day steroid therapy is innocuous or can be used without discretion and close supervision. Furthermore,

the studies are focused on adrenal function only as determined by exogenous ACTH stimulation and do not necessarily represent the status of the entire hypothalamic-pituitary-adrenal axis. However, the data in this study do imply that, in children with severe asthma who require long-term corticosteroid therapy, an alternate-day regimen with the use of prednisone significantly minimizes the development of adrenal suppression, the most serious side effect of steroid administration.

SUMMARY

Three investigative studies of corticosteroid-induced adrenal suppression indicate that: (1) Alternate-day prednisone produces less adrenal suppression than the stated equivalent doses of alternate-day dexamethasone in asthmatic children treated for 6 weeks. (2) Adrenal stimulation one hour after injection of synthetic ACTH (Cortrosyn) is equivalent to that two hours after injection of natural ACTH. (3) Long-term alternate-day treatment of asthmatic children with prednisone does not ordinarily induce adrenal suppression as measured by the ACTH response test.

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