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PLASMA CORTISOL RESPONSES TO CORTROSYN TREATMENT IN ASTHMATIC CHILDREN

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Summary

Treatment trial over a period of 3 months was conducted with intermittent intramuscular injections of Cortrosyn depot in fourteen children with severe and frequent asthmatic attacks.

The basal plasma cortisol levels were generally high, but higher than normal in four (29%) of the patients. At a period of 24 h after the initial Cortrosyn injection was administered, plasma cortisol increases ranging between 4 – 52 µg/100 ml above the basal levels were recorded. At a period of 1 week after the end of daily injections for 1 week, increases of plasma cortisol ranging between 3 – 71 µg/100 ml above the basal levels were observed and presumed to be a reflection of an associated adrenal hypertrophy resulting from repetitive daily Cortrosyn injections. The highest increases at this stage were observed in the youngest patients with the severest asthmatic attacks, but not in their older counterparts.

At the end of the trial treatment, clinical improvement was associated with lowered plasma cortisol levels compared with the elevated basal values.

Resumé

Un titre d'essai couvrant une période de trois mois, on a pratiqué un traitement avec des injections intramusculaires intermittentes de dépôt de cortrosyne à quatorze enfants présentant des attaques asthmatiques fréquentes et aigües.

Les concentrations initiales de cortisol de plasma furent généralement fortes, mais plus fortes qu'à l'état normal chez 4 (29%) des malades. Depuis un periode de 24 h après la première injection de cortrosyne on a enregistré des augmentations de cortisol de plasma varient entre 4 – 52 mg/100 ml au dessus des concentration initiales. Une semaine après les injections journalières qui avaient duré une semaine, des augmentations du cortisol de plasma, varient entre 3 – 71 mg/100 ml au dessus des concentrations initiales, furent observées et considerées comme étant le reflect d'une hypertrophie surrénale associée, résultant d'injections journalières répétées de cortrosyne. Les augmentations les plus notoires à ce stade furent observées chez les plus jeunes patients présentant des attaques asthmatiques les plus aigües, mais pas chez les autres malades plus âgés.

A la fin de cet essai de traitement, on a relié le progrès médical à la comparaison entre les faibles et les fortes concentrations de cortisol de plasma.

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Introduction

Tetracosactrin (Cortrosyn) depot is an effective and potent stimulant of adrenal function, when given intramuscularly or subcutaneously, it has a prolonged action lasting over 24 h at a dose of 1·0 mg (Nelson *et al.*, 1968). These authors have expressed optimistic views about its use in the maintenance treatment of selected patients with rheumatoid arthritis or bronchial asthma.

This paper reports the plasma cortisol response

in fourteen children with severe and frequent attacks of bronchial asthma who were partaking in a therapy trial with the synthetic corticotrophin (tetracosactrin depot).

Patients and methods

Fourteen children aged between 2·5 and 11 years (mean 7·9 years) with severe and frequent attacks of bronchial asthma, who were no longer responding adequately to bronchodilators, were admitted to the trial which lasted for a period of 18 months. They were classified into two groups according to their responses to the treatment:

Group 1a consisted of three patients with severe asthmatic attacks who did not require further treatment during the 12-month period of observation after the trial.

Group 1b consisted of five patients with moderately severe asthmatic attacks who required only minimal use of bronchodilators during the observation period after the trial.

Group 11a consisted of three patients with severe asthmatic attacks who required continuous maintenance therapy with cortrosyn.

Group 11b consisted of three patients with moderately severe asthmatic attacks who required continuous treatment with bronchodilators during the 12-month period of observation after the drug trial.

Blood samples were collected at 9 a.m. for the basal plasma cortisol estimation, followed immediately by administration of the initial dose of Cortrosyn depot. Twenty-four hours later, at 9 a.m., second samples of venous blood were obtained for cortisol estimation. This was followed by daily injections of Cortrosyn for 1 week, after which blood samples were collected at 9 a.m. on the next clinic day, exactly 1 week after the last of the daily injections. Thereafter Cortrosyn injection was tapered off, being administered once a week for 2 weeks and once fortnightly for 2 months. The final blood samples were collected a week after the last injection. Plasma cortisol was measured fluoremetrically by the method of Mattingly (1962).

The dose of Cortrosyn depot given ranged between 0·125 – 0·5 mg intramuscularly according to the age of the patient.

Result

High plasma cortisol ranging between 5–50 µg/100 ml (mean 25·1 µg/100 ml) were recorded for basal values; four patients (29%) have higher values than the normal of 6·0 – 28 µg/100 ml. Plasma cortisol values rose to values ranging between 27 – 89 µg/100 ml (mean 43·9 µg/100 ml), representing increases of between 4·0 – 52 µg/100 ml above basal levels 24 h after the initial Cortrosyn injection.

One week after the daily injection of Cortrosyn for 1 week, plasma cortisol ranged between 12 – 86 µg/100 ml (mean 35·5 µg/100 ml), representing increases between 3 – 71 µg/100 ml over the basal value. At the end of the trial, 3 months later, plasma cortisol levels ranged between 2·0 – 30 µg/100 ml (mean 11·8 µg/100 ml).

Discussion

Generally, in this series, basal plasma cortisol levels were high, ranging between 5 – 50 µg/100 ml with a mean of 25 µg/100 ml. Two of the three patients with severe attacks in Group 11a had the lowest and highest basal plasma cortisol values of 5 – 50 µg/100 ml. The generally high basal plasma cortisol levels may, at least, in part be related to the stress of status asthmaticus (El-Shaboury, 1966), however elevated levels at 24 h after stimulation with Cortrosyn injections indicate that the adrenal glands had not been previously maximally stimulated in any of the patients, except probably one patient (A.A.) aged 4·5 years who had a basal level of 50 µg/100 ml. Definite conclusion on this would have been possible, if the 8 h post-stimulation blood sample had been obtained for cortisol estimation, since the peak of response of plasma cortisol was expected thereabout (Nelson *et al.*, 1968). One patient (A.A.) aged 4·5 years was one of the three patients who were kept on maintenance therapy with Cortrosyn because of the lack of satisfactory response during the trial. Similarly, abnormally high, but relatively lower basal plasma cortisol values were recorded for three other patients, two of which later required continuous treatment with bronchodilators. Thus, three (75%) of the four patients, whose basal plasma cortisol levels were abnormally elevated, consequently either received continuous treatment with bronchodilators or maintenance therapy with Cortrosyn. From this result, one would be tempted to establish a relationship between the basal plasma cortisol and the response to Cortrosyn treatment.

TABLE 1. Group 1a, those who did not require any further treatment and Group 1b, those who required only minimal bronchodilator treatment

Group	Patients	Age in Years	Plasma cortisol (µg/100 ml) Basal	24 h after Cortrosyn	After daily injection for 1 week	End of Cortrosyn injection 3 months later
1a	Severe attacks					
	E.E.	10	20	40	—	14
	O.O.	10	27	48	33	15
	T.I.	9	20	36	30	30
	Mean	9.7				
1b	Moderately severe attacks					
	I.T.	9	10	27	15	24
	A.A.	3	37	89	12	10
	S.O.	8·5	28	52	32	22
	O.O.	10·5	27	53	—	5
	S.T.	11	20	29	23	8
	Mean	8·4				

TABLE 2. Group 11a, those maintained on cortrosyn therapy and Group 11b, those who required continuous bronchodialator treatment

Group	Patients	Age in Years	Plasma cortisol (µg/100 ml) Basal	24 h after Cortrosyn	After daily injections for 1 week	End of Cortrosyn injection 3 months later
11a	Severe attacks					
	A.O.	6	23	51	86	5
	A.A.	4·5	50	34	—	18
	C.O.	4·5	5	36	76	7
	Mean	5·2				
11b	Moderately severe attacks					
	B.A.	11	31	43	17	2
	B.T.	2·5	23	42	31	20
	I.I.	11	30	34	—	5
	Mean	8·2				

In the two groups, patients with severe and moderately severe asthmatic attacks were almost equally represented, however, considering their mean ages, those in Group a and b were 9·7 and 8·4 years old respectively. The corresponding figures for those in Group 11a and b were 5·0 and 8·2 years. In spite of their initial severe asthmatic attacks, the response to treatment in Group 1a was most satisfactory, thus no further treatment was required during the 12-month period of observation after the trial and only minimal treatment with bronchodilators were required for those in Group 1b. On the other hand, those with severe asthmatic attacks in Group 11a had the least satisfactory response to the trial treatment and thus required maintenance therapy with Cortrosyn. Those in Group 11b required continuous treatment with bronchodilators. Although the severity of the asthmatic attacks in both groups were of equal and comparable magnitudes, there was an obvious age disparity, particularly between Groups 1a and 11b, which probably modified their responses to the treatment. Those who required maintenance Cortrosyn therapy were the youngest with a mean age of 5·0 years, followed by Groups 1b and 11b who required minimal and continuous treatment with bronchodilators respectively. Their mean ages of 8·4 and 8·2 years respectively are almost identical. Regardless of the severity of their asthmatic attacks, those in Group 1a were the oldest with a mean age of 9·7 years. They responded most satisfactorily to the Cortrosyn trial treatment.

Cortisol levels of plasma samples obtained 1 week after the last of the daily injections for 1 week, were observed to be higher than the basal levels in five patients and much higher still in two of the three patients who later had to be placed on Cortrosyn maintenance therapy. The plasma cortisol level for the third patient was, however, not available. The sustained elevation of plasma cortisol at this point in time was probably related to adrenal hypertrophy consequent upon repetitive injections of Cortrosyn (Daly & Glass, 1971). While adrenal hypertrophy would be expected at the end of the week-long injection of Cortrosyn, gradual and variable regression of the hypertrophied glands would therefore be expected to follow the cessation of the injection. Plasma cortisol estimated 1 week after the serial injections still revealed some evidence of residual glandular hypertrophy in terms of minor increases of plasma cortisol over the basal levels ranging between 3·0 – 10 μg/100 ml (mean 6·4 μg/100 ml) in 5 patients in Groups 1a and 1b. Values ranging between 63 – 71 μg/100 ml (mean 67 μg/100 ml) were recorded for Group 11a who required maintenance Cortrosyn therapy. The significance of the sustained phenomenal increase, particularly in those who later required maintenance therapy, was not clear except that one could only infer a greater degree of adrenal hypertrophy in the patients than the others.

The final plasma cortisol values were obtained from samples of blood collected 1 week after the third series of Cortrosyn injections. At this stage, all plasma cortisol values had fallen beyond the basal levels. Greater fall to lower than 30% of the basal levels was observed in those who required continuous treatment with bronchodilators and those maintained on Cortrosyn therapy, except one patient (C.O.) who already had a very low basal plasma cortisol. On the contrary, lesser fall in plasma cortisol values to levels not beyond 50% of the basal values were observed in those in Groups 1a and 1b with the exception of Patients (T.I.) and (I.T.) who still maintained higher values over their respective basal levels.

The diminished final plasma cortisol values below the basal levels may be a reflection of endogenous corticotropin suppression (Daly & Glass, 1971). Although there are conflicting reports on the suppressive effects of ACTH on the hypothalamo-pituitary-adrenal axis, Bacon *et al.* (1968) and Carter James (1970) are convinced of the existence of a temporary suppression of the axis. It was observed in this series that those who required continuous treatment with bronchodilators and those maintained on Cortrosyn therapy showed relatively more evidence of suppression of the hypethalamo-pituitary-adrenal axis with respect to their final plasma cortisol levels than those who did not require further treatment as well as those who required only minimal use of bronchodilators. The values of plasma cortisol of the samples obtained after the serial daily injections for 1 week did not signify any suppression of the axis, because of the compensatory increase of cortisol production from hypertrophied adrenal glands (Daly & Glass, 1971).

It is significant to note that the clinical improvement in the conditions of all the asthmatic children in this series were associated with lowered, final plasma cortisol levels compared to their elevated basal levels. Could there possibly have been a resetting of the hypothalamo-pituitary-adrenal axis to an advantage?

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