Recovery of Adrenocortical Function During Long-term Treatment with Corticosteroids

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Summary: The recovery of adrenocortical function during very slow withdrawal of corticosteroids was studied in a homogeneous group of patients suffering from sarcoidosis. All patients had been treated with gradually decreasing doses of prednisone for at least two years. The initial dose had been 40 mg. daily in all cases. Determination of the cortisol production rate and of plasma fluorogenic corticosteroids was done under basal conditions and after tetracosactrin stimulation. There was good correlation between cortisol production rate and plasma fluorogenic corticosteroids throughout all the tests. Cortisol production rate and plasma fluorogenic corticosteroids started to rise when the dosage of prednisone was lowered to 7.5 mg. daily and reached normal values when the dosage was reduced to 2.5 mg. The response to tetracosactrin began to increase at the same dosage level, but was not normal at 2.5 mg., or when prednisone treatment was stopped. At a dosage level of 7.5 mg. of prednisone plasma fluorogenic corticosteroids already showed a nyctohemeral rhythm. It may be calculated that even very low dosages of prednisone given during the last stage of a treatment schedule enhance total corticosteroid activity beyond the normal level, which would account for their therapeutic value.

Introduction

The present study was undertaken to investigate the recovery of adrenocortical function during very slow withdrawal of corticosteroids in a homogeneous population of patients who had been on this therapy for a number of years. Furthermore, we aimed to ascertain whether the very low dosages of prednisone given during the last stages of such a treatment were therapeutically active. The 43 subjects who participated were part of a large group of patients suffering from pulmonary sarcoidosis who had been treated with prednisone for at least two years according to a uniform schedule (shown in Table I). Besides determining the plasma fluorogenic corticosteroids, as usually undertaken in similar investigations, we measured the cortisol production rate by isotope dilution, in order to obtain the most reliable quantitative assessment of adrenocortical function.

In a pilot study the cortisol production rate was determined at a time when the dosage of prednisone had been decreased to 12.5 mg. or less. Further investigations, including measurement of plasma fluorogenic corticosteroids in the morning and afternoon and the cortisol production rate and plasma fluorogenic corticosteroids during and after tetracosactrin stimulation, were made on 26 patients when they had reached a dosage level of 7.5 mg. of prednisone or less. All investigations were made after the dosage level indicated in the charts had been maintained for at least four months. In addition, eight of these patients were studied within six months after cessation of treatment. In 18 patients the cortisol production rate could be determined more than once.

Patients and Methods

The diagnosis of sarcoidosis was confirmed in all patients by extensive laboratory examinations, x-ray studies, and biopsies (lymph nodes, liver, lung, and skin, or bronchial mucosa, or several). Details concerning diagnostic procedures and indications for corticosteroid therapy have been described elsewhere (Deenstra and Van Ditmars, 1968).

Of the patients studied 22 were men aged 25-63 and 21 were women aged 27-63. Twenty-seven were in hospital for six days. On the second day the cortisol production rate was determined; plasma fluorogenic corticosteroids were measured at 8.30 a.m. and 4.30 p.m. on days 3 and 4. On day 5 the patients received an intravenous infusion of 0.25 mg. of tetracosactrin (Synacthen) in 500 ml. of saline during eight hours. On the same day the cortisol production rate was again determined. Plasma fluorogenic corticosteroids were measured at the beginning and at the end of the infusion. Prednisone treatment was continued during all tests. Furthermore, 29 patients aged 20-61 with pulmonary sarcoidosis were investigated before prednisone treatment was started—in six the whole series of tests were done and in 23 the cortisol production rate only. For comparison the cortisol production rate was determined in 23 normal volunteer subjects (staff...

| Table I.—Schedule for Treatment with Prednisone of Patients with Sarcoidosis. Treatment Starts with 40 mg. of Prednisone Daily during the Time Indicated followed by a Gradually Decreasing Dose, as shown from Top to Bottom. Total Time of Prednisone Medication is about 6 Years |
|---|---|---|---|---|---|---|---|---|---|---|
| Dosage per day |
| - | 40 mg. of prednisone |
| - | 20 mg. |
| - | 15 mg. |
| - | 10 mg. |
| - | 5 mg. |
| - | 5 mg. |
| - | 5 mg. |
| - | 2.5 mg/2 days |
members, students, and laboratory technicians) aged 20-45 years. Normal values for morning and afternoon plasma fluorogenic corticosteroids were obtained from 27 subjects aged 20-45 and normal values for plasma fluorogenic corticosteroids after tetracosactrin stimulation from 10 subjects aged 28-59.

Cortisol production rates were determined by a modification of the method of Cope and Black (Thijssen et al., 1967). Plasma fluorogenic corticosteroids were measured fluorometrically (Mattingly, 1962).

Results and Discussion

The cortisol production rates are shown in Fig. 1; those relating to patients in whom more than one determination could be done are connected by a line. A rise in the values can be seen when a dosage level of 7.5 mg. of prednisone is reached. At a level of 2.5 mg. the values are in the same range as those found in the normal subjects and in the untreated patients. The course of the longitudinal observations generally fits quite well into the overall picture.

The plasma fluorogenic corticosteroid values (Fig. 2) show a trend similar to that of the cortisol production rate. Here too the normal range is reached at a dosage level of 2.5 mg. of prednisone, both for the morning as well as for the afternoon values. Data reported in the literature on cortisol values in plasma during and after corticosteroid treatment are contradictory. After sudden withdrawal of corticosteroids normal values were found by Robinson et al. (1962) in 16 out of 17 patients and by Livanou et al. (1967) in only 8 out of 26 patients. Graber et al. (1965) made a serial study in 14 patients from whom the corticosteroids had been withdrawn within one to four weeks. For several months they found plasma fluorogenic corticosteroids were depressed and plasma adrenocorticotropic hormone (A.C.T.H.) raised. Results similar to those shown in Fig. 2 were reported by Daly et al. (1967). There are few data on cortisol production rates (Robinson et al., 1962; Kilborn and Robson, 1965), and those reported do not allow comparison with our data, as the design of the investigations was different.

From our studies it can be concluded that during very gradual withdrawal of corticosteroids the plasma fluorogenic corticosteroid concentration becomes normal and that the basal adrenocortical function as measured by the cortisol production rate returns to normal while prednisone treatment is continued at a low dosage. The fact that even at a very early stage of adrenocortical recovery, at a dosage level of 7.5 mg. of prednisone, a definite nyctohemeral rhythm can be seen (Fig. 2) shows that pituitary A.C.T.H. secretion is resumed in a rhythmic manner. This corroborates the finding of Graber et al. (1965) of nyctohemeral variations of plasma A.C.T.H. in patients in whom the adrenal was still suppressed. In contrast to this Retiene et al. (1966) found that the daily variations in plasma A.C.T.H. were abolished two days after withdrawal of prednisone.

The recovery of the adrenocortical response to tetracosactrin is shown in Fig. 3 for the cortisol production rate and in Fig. 4 for plasma fluorogenic corticosteroids. There is a linear correlation between the recovery of the basal function and that of the response to tetracosactrin. Nevertheless, in contrast to the basal function, the response to tetracosactrin is not normal at the level of 2.5 mg. of prednisone, and even after stopping treatment only about half of the patients reacted normally to stimulation. This difference is shown in Table II, which summarizes the incidence of normal responses. It would appear from these studies that on reduction of the prednisone dosage to less than 10 mg. the pituitary resumes rhythmic A.C.T.H. secretion, which in its turn leads to complete recovery of the adrenal as shown by a normal response to tetracosactrin stimulation. It must, however, be realized that in our study stimulation tests were done using more than physiological amounts of tetracosactrin. The possibility cannot be excluded that the reaction of the adrenal to physiological stimuli might be different.

There is no need to measure this response with the elaborate and expensive isotope dilution method. In our survey the correlation between the results of cortisol production rate and
of plasma fluorogenic corticosteroid estimations was excellent \((r=0.90)\) (Fig. 5). The use of either a long-acting corticotrophin preparation or of a tetracosactrin infusion, which in our experience and that of Nuki et al. (1969) gives the same results, might be preferable to a half-hour test as used by Wood et al. (1965), Daly et al. (1967), and Jasani et al. (1967). The recovery of the adrenal cortex must be due to an essentially normal basal function of the hypothalamic-pituitary system. The question remains whether its reaction to stress will be equally adequate. Jasani et al. (1968) compared the response of the adrenal to tetracosactrin with that to insulin-hypoglycaemia, metyrapone, and pyrogens. Several patients who showed a normal rise of plasma fluorogenic corticosteroids after tetracosactrin reacted poorly to the other stimuli. These patients showed less rise in plasma cortisol during orthopaedic surgery, but in all cases in which the response to tetracosactrin was normal the operation was tolerated without the need for corticosteroids.

Sampson et al. (1962) subjected patients who had been treated with corticosteroids for ulcerative colitis to abdominal surgery. The therapy had been stopped a few days before operation. Corticosteroids were given during surgery only to those who showed an insufficient response to corticotrophin. In 40 patients who had recently stopped steroid treatment Plumptre et al. (1969) found a normal response of the plasma corticosteroids to surgery. To evaluate the total biological corticosteroid activity to which the patient is exposed, we have expressed cortisol production rates per square metre of body surface (Fig. 6). The arithmetical means of the groups are connected by a line, representing the rise of endogenous corticosteroid activity. The dosage of prednisone was converted into its cortisol equivalent by using the factor 4. The broken line in the figure represents the sum of the endogenous and the calculated exogenous corticosteroid activities. Evidently even at the dosage level of 2.5 mg of prednisone this total activity is much higher than that found in normal subjects.

From these data the therapeutic action of very small amounts of corticosteroids under the conditions studied can easily be understood. Shuster and Williams (1961) came to similar conclusions from determinations of urinary corticosteroid metabolites, but their patients had not been on prolonged corticosteroid therapy.

All patients in our study were suffering from sarcoidosis. Could the nature of the disease have influenced the results? Gray and Shaw (1965) studied the cortisol metabolism in patients with sarcoidosis, but did not find significant alterations in the peripheral metabolism of cortisol. In their four patients studied before treatment with corticosteroids, however, the cortisol production rate was in the lower normal range. In our survey (Fig. 1) there is a difference between the cortisol production rate of the healthy control subjects and that found in the untreated patients with sarcoidosis, the latter being lower. The difference, though small, is statistically significant \((P=0.01)\); Wilcoxon test), but there is also a difference in age distribution between the two groups, the patients with sarcoidosis being older. As the cortisol production rate decreases with age (Romanoff et al., 1961) we do not think that the difference in cortisol production rate can be attributed to the disease.

Finally, did the continuation of prednisone treatment during the tests influence the results? Prednisone or its metabolites are not measured by the fluorescent method (Matringly, 1962), and their contribution to the cortisol production rate may be assumed to be at the most 3% of the dosage given—calculated from the data of Vermeulen (1959).
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REFERENCES

Medical Memoranda

High Serum Acid Phosphatase Values in a Case of Lymphoblastic Leukaemia

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In a patient with acute lymphoblastic leukaemia and a greatly increased serum acid nitrophenylphosphatase activity, as measured with the Sigma procedure (Sigma Technical Bulletin No. 104, revised August 1961), disappearance of blast cells from the bone marrow, and the blood after chemotherapy was followed by the return of serum acid phosphatase levels to normal. Relapse was again accompanied by a rise in enzyme levels.

CASE HISTORY

A 55-year-old man was referred to the Institut Jules Bordet in September 1965 because of right cervical and axillary masses of three months' duration. Physical examination showed several firm, non-tender cervical and axillary lymph nodes measuring 3–5 cm. Haemoglobin was 12 g./100 ml., and white cell count 4,900 with a normal differential; platelets were 102,000/mm³, and bone marrow showed 4% lymphoblasts. Biopsy of an axillary lymph node showed lymphoblastic lymphosarcoma. Pathology to the right cervical and axillary areas was followed by complete disappearance of the enlarged lymph nodes.

In December several bilateral supraclavicular, axillary, and inguinal nodes varying from 0-5 to 3 cm in diameter were found. Palpation of the sternum was painful. The lower edge of the spleen was felt 8 cm. below the left costal margin. Rectal examination showed a normal prostate. The haemoglobin was 9 g./100 ml., the white cell count 20,000 with 51% blasts, and the platelet count 72,000/mm³. The blood leucocyte alkaline phosphatase score was 118/100 cells. Bone marrow aspiration yielded 58% blasts. Serum alkaline phosphatase was normal at 1.6 Sigma units, but the acid phosphatase values were repeatedly between 4 and 8 Sigma units, this activity being inhibited by the addition of L-tartrate.

Intravenous administration of 160 mg. of methylprednisolone daily for three weeks produced no beneficial effect. The treatment was discontinued because of gastric bleeding. Vincristine in doses of 1.5 mg. was given intravenously at weekly intervals. Within five days after the first injection the blasts in the peripheral blood dropped from 60% to 2%, while the white cell count fell from 64,000 to 1,000. The spleen was no longer felt. The acid phosphatase level dropped to a normal value of 0.4 Sigma units/100 ml. of serum. For two months no blasts or other immature cells were found in the blood or in the bone marrow, and the serum acid phosphatase values remained normal (see Chart).

Early in April 1966 the spleen was again palpable. The white cell count was 3,700 with 17% blasts and the platelet count was 60,000. Bone marrow examination revealed 5-5% blasts. The serum acid phosphatase was found to be raised again at 2 Sigma units. The dosage of vincristine was increased to 3.5 mg. weekly, and methylprednisolone 180 mg. daily was administered for three weeks. The spleen had become impalpable, blasts in the peripheral blood and in the bone marrow dropped to 2%, and the platelet count and serum acid phosphatase levels returned to normal.

In June generalized lymph nodes and a large spleen were again palpable. Bone marrow aspiration yielded 60% blasts. The white cell count was 14,800 with 57% blasts and the platelet count was 1,000. Serum acid phosphatase activity was 7-4 Sigma units and was reduced to 0.8 unit in the presence of L-tartrate. The white cell count fell to 600 and the serum acid phosphatase value dropped to nearly zero. On 10 July the patient died after a massive haematuria. Post-mortem examination showed leukemic infiltrates in the spleen, bone marrow, and latero-tracheal nodes. Examination of the prostate failed to show carcinoma or leukemic infiltrates.

COMMENT

A consistent increase in serum acid phosphatase values was observed when the leukaemia was progressive and the number of blasts in the blood and bone marrow rose. In contrast, during the periods of remission with normal bone marrow and blood the serum acid phosphatase values were also normal. Raised acid phosphatase values in the serum of a patient with lymphoblastic leukaemia has not been reported*.

* Serum acid phosphatase was measured at pH 4.8 by using paranitrophenylphosphate as a substrate, following Sigma procedure (normal 0.63 u./ml. in the male) (Sigma Technical Bulletin No. 104, revised 8 August 1961).