Adrenal Failure Complicating Status Asthmaticus in Steroid-treated Patients

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Though pathological studies have shown that administration of adrenal steroids can cause adenocortical atrophy in experimental animals (Ingle, 1938; Winter et al., 1950; Rawls et al., 1954; Holub et al., 1959) and in man (Sprague et al., 1950, 1951; Salassa et al., 1953; Bennett, 1954; Stoner and Whiteley, 1954), biochemical studies have revealed that the adrenal glands are capable of responding satisfactorily to corticotrophin (A.C.T.H.) stimulation despite many years of steroid therapy (Fredell et al., 1955; Larzelere et al., 1957; Carreon et al., 1960; Andersson and Kjerulf, 1961; Robinson et al., 1962; Savage et al., 1962; Brink-Johnsen et al., 1963; Treadwell et al., 1963). Even when a subnormal increase in plasma 17-hydroxysteroids (17-OHCS; cortisol) is found during an infusion of A.C.T.H., a significant increase has been recorded with more prolonged adrenal stimulation (Eik-Nes et al., 1955; Christy et al., 1956; Sandberg et al., 1957; Kruisius and Oka, 1958; Landon et al., 1965).

There do not appear to be any reports on adrenal function during attacks of status asthmaticus in patients receiving long-term steroid therapy. The present paper describes the plasma 17-OHCS response to the administration of A.C.T.H. in 17 such patients with status asthmaticus.

Material and Methods

Seventeen patients (14 women aged 25 to 78, mean 51.5 years, and three men aged 29, 52, and 53) were studied. The duration of asthma ranged from 2 to 40 years, and continuous steroid therapy had been given over periods ranging from 5 to 86 months, mean 38.2 months. All patients were known asthmatics who had regularly attended the asthma clinic at Cardiff. They were admitted to hospital in status asthmaticus, a condition previously defined (El-Shaboury et al., 1964). Three patients were investigated during two separate attacks of status asthmaticus.

On admission all patients received 0.5 ml. of adrenaline administered subcutaneously at intervals of 10 to 15 minutes for three doses, followed by 0.5 g. of intravenous aminophylline. About 15 to 30 minutes later the patient’s condition was again evaluated. When there was no improvement, as indicated by continued respiratory distress and persistent tachycardia (above 110 per minute), treatment with A.C.T.H. was started. This consisted of an intravenous infusion containing 40 to 230 units of A.C.T.H. given over periods ranging from 4 to 40 hours. At the end of A.C.T.H. infusion intramuscular injections of 40 units A.C.T.H.-gel were administered at intervals of 4, 6, 8, or 12 hours for a minimum period of three days. The total dose of A.C.T.H. given intramuscularly during these three days varied from 240 to 560 units. The duration of the infusion and frequency of intramuscular A.C.T.H. injections were determined according to the clinical condition of the patient. Persistent tachycardia (Williams, 1963) and respiratory distress were a guide to the severity of the attack and response to treatment. No adrenal steroids were given.

Plasma 17-OHCS values were determined immediately before and at hourly intervals during A.C.T.H. infusions for a minimum period of four hours. In eight patients the plasma 17-OHCS concentration was again determined five hours after each morning injection of A.C.T.H.-gel. Plasma 17-OHCS was estimated at the end of the study by the method of Peterson et al. (1957) with the modification suggested by Hatfield and Shuster (1959).

In normal subjects plasma 17-OHCS concentration was found to range from 7 to 28 μg./100 ml., with a mean of 17.2 μg., 5.9 S.D. In 10 asthmatic females who had not received steroid therapy and who were studied while free from asthmatic symptoms, to serve as controls, the administration of an intravenous infusion containing 40 units of A.C.T.H. over four hours resulted in plasma 17-OHCS concentration ranging from 35 to 53 μg./100 ml. Values between 40 and 88.5 μg. were recorded during subsequent intramuscular injections of 40 units of A.C.T.H.-gel administered every 12 hours for three days.

Results

The Table shows the plasma 17-OHCS results of the 17 patients studied, their previous steroid therapy, and the quantity of A.C.T.H. given during the first three days in hospital. The interval of time between the last dose of steroids and the start of A.C.T.H. infusion is also shown. With the exception of two patients (Cases 3 and 17), steroid therapy was continued to within 48 hours or less of administration of A.C.T.H.

It can be seen that the plasma 17-OHCS results in Cases 1–3 were low both before and during A.C.T.H. administration and contrast strongly with those recorded in the rest of the group. During the next three days of intramuscular injections of A.C.T.H.-gel a slight increase in plasma 17-OHCS was recorded, but the values were well below the minimal response obtained in control asthmatic subjects (40 μg./100 ml.). Similarly Cases 2 and 3 showed little if any increase in plasma 17-OHCS during the three-day period of stimulation with A.C.T.H. When adrenal function was again evaluated in Case 2, during his second admission to hospital, no increase in plasma 17-OHCS was recorded.

It can also be seen from the Table that a subnormal plasma 17-OHCS response to A.C.T.H. was recorded in Cases 4 and 5 and the value obtained in Case 6 was just below the minimum response to A.C.T.H. infusion found in control subjects (35 μg./100 ml.). In Case 4 there was little increase in plasma 17-OHCS over basal values during the infusion of A.C.T.H., but the values during the subsequent three days of A.C.T.H. stimulation approached the minimal response witnessed in the control group, indicating recovery of adrenal function.

The remaining 11 patients had normal or increased plasma values. In 9 of them (Cases 7 to 11) plasma 17-OHCS concentration determined immediately before A.C.T.H. infusions (0 hour) was increased above the upper limit of normal (28 μg./100 ml.), and there was a further increase during stimulation with A.C.T.H. In seven patients the plasma 17-OHCS response to A.C.T.H. infusion was similar to that recorded in the control group, and in four patients (Cases 8, 10, 11, and 17) this was increased.

The chart shows the mean and standard deviation for plasma 17-OHCS values in the patients with status asthmaticus and in
the 10 control asthmatic subjects. The results recorded in Cases 1–3 are shown separately. It is apparent from the chart that these three patients failed to respond to A.C.T.H. stimulation. In the 14 patients who showed a response to A.C.T.H. the mean plasma 17-OHCS was higher than that recorded in the control group at 0 hour and during the first three hours only of A.C.T.H. infusion. On the second and third days of intramuscular A.C.T.H. injections the mean was reduced, but during this period it represents the plasma values of only 5 of the 14 patients.

The progress in hospital of the three patients with adrenal failure is given below.

**Case 1**

A man aged 53 with intrinsic asthma took 1 mg. of betamethasone daily for 55 months up to seven hours before admission to hospital in status asthmaticus. Despite the administration of A.C.T.H. infusion over a period of 40 hours, followed by injections of 40 units of A.C.T.H.-gel every four hours, severe breathlessness persisted, and the pulse rate remained around 120 for five days. The blood pressure was 120/90 mm. Hg.

On the sixth day he began to improve, and repeated asthmatic attacks were reasonably controlled with injections of adrenaline and aminophylline. The lung-function tests remained poor: forced expiratory volume (F.E.V.1) 750 ml., forced vital capacity (F.V.C.) 1,300 ml., and peak expiratory flow rate (P.E.F.R.) 75 litres per minute. Arterial Po2 was 67 and Pco2 43.8 mm. Hg. Between the thirteenth and sixteenth days his symptoms became progressively worse. The administration of intravenous injections of 20 units of A.C.T.H. on three occasions resulted in the development of severe and alarming hypersensitivity reactions (El-Shaboury, 1965).

Treatment with adrenal steroids was then given, and he steadily improved: F.E.V. 1,800 ml., F.V.C. 2,300 ml., and P.E.F.R. 245 l./min. He has remained well on 1.5 mg. of betamethasone daily.

**Case 2**

A man of 29 with intrinsic asthma discontinued his usual dose of prednisone (10 mg./day for 41 months) because of persistent vomiting 48 hours before admission to hospital in status asthmaticus. The pulse rate was 160 and blood pressure 110/70 mm. Hg. A.C.T.H. infusion was given for 15 hours, followed by injections of 40 units of A.C.T.H.-gel every four hours. He remained ill for three days, and on the fifth day his lung-function tests were still low: F.E.V. 1,200 ml., F.V.C. 3,200 ml., and P.E.F.R. 125 l./min. Arterial Po2 and Pco2 were 78.4 and 41.1 mm. Hg respectively. Severe asthmatic attacks occurred, and prednisone therapy was restarted.

Three months later he was readmitted to hospital with progressively severe attacks of asthma for 48 hours. The pulse rate rose to 150, and the F.V.C., measured by a specially adapted spirometer, was only 500 ml. The results of plasma 17-OHCS determined during his first admission to hospital were not available, and an infusion of A.C.T.H. was started. He remained very dyspnoeic, sweated profusely, and vomited on two occasions. The F.V.C. fell to 300 ml., the pulse rate was 160, and blood pressure 110/80 mm. Hg. He was immediately given 300 mg. of hydrocortisone intravenously. His general condition improved within 15 minutes, the vomiting stopped, pulse rate fell to 140, and he became rational. Prednisone was given by mouth, initially every two hours, and he made a steady recovery over the subsequent three days. He has remained well on 15 mg. of prednisone per day: F.E.V.1 2,300 ml., F.V.C. 5,000 ml., and P.E.F.R. 270 l./min.

**Case 3**

A woman aged 52 with intrinsic asthma received 10 mg. of prednisone daily for 61 months. She was admitted to hospital in July 1963 for investigation of haemoptysis during an attack of asthma. Steroid treatment was not continued, and on the sixth day she felt unwell, with epigastric pain, vomiting, and persistent attacks of asthma. The pulse rate averaged 110 and the systolic blood pressure ranged between 100 and 110 mm. Hg. Lung-function tests were: F.E.V.1 700 ml., F.V.C. 1,200 ml.

On the twelfth day she was in status asthmaticus, pulse 130, blood pressure 100/60 mm. Hg. Adrenaline and intravenous aminophylline had little if any effect, and an infusion of A.C.T.H. was begun. Ten minutes later she collapsed, became unconscious, and the pulse and blood pressure could not be recorded. With injections of nikethamide, adrenaline, vasopressor agents, artificial respiration, and oxygen she regained consciousness after approximately 15 minutes. The blood pressure was maintained with repeated injections of metaraminol and mephentermine sulphate during the sub-

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**Plasma 17-OHCS During A.C.T.H. Stimulation in Patients with Status Asthmaticus who have Received Continuous Steroid Therapy**

| Case No. | Age | Sex | Duration of Asthma (yr.) | Duration of Injections (Months) | Steroids | A.C.T.H. Therapy* | Continuous Steroid Therapy | Plasmas 17-OHCS Values (µg. /100 ml) | After Intramuscular Injection
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* During first 3 days in hospital. † Five hours after each morning injection. B = Betamethasone. P = Prednisone. T = Triamcinolone.
sequential five hours. A.C.T.H. infusion was continued for 16 hours, followed by injections of 40 units of A.C.T.H.-gel every four hours for a period of five days.

She began to improve after 48 hours, but continued to have asthmatic attacks with a persistent pulse rate of 100 to 110 per minute. The lung-function tests remained low: F.E.V.: 650 ml., F.V.C. 1,100 ml. When prednisone was given the asthmatic attacks were controlled. She has remained well on a maintenance dose of 15 mg. of prednisone daily: F.E.V.: 1,700 ml., F.V.C. 2,300 ml., and P.E.F.R. 210 L/min.

Discussion

Failure of the adrenal glands to respond to A.C.T.H. treatment during the management of status asthmaticus has not been demonstrated previously. The present study shows that of 17 patients who had received long-term steroid therapy three were suffering from adrenal failure despite adequate stimulation with A.C.T.H. for three days. Persistently low plasma 17-OHCS values were recorded, and failure of adrenal response to A.C.T.H. was again found in one of these patients during a subsequent attack of status asthmaticus. When these three patients were free of asthmatic symptoms re-evaluation of adrenal function confirmed the presence of adrenal suppression, and the results in Case 1, who developed hypersensitivity reactions to A.C.T.H., have already been published (El-Shaboury, 1965). The finding of a diminished adrenal response to A.C.T.H. infusion in three other patients with status asthmaticus is in agreement with previous reports on adrenal function in steroid-treated patients with various disorders (Eik-Nes et al., 1955; Christy et al., 1956; Sandberg et al., 1957; Krusius and Oka, 1958; Marks et al., 1959; Shuster and Williams, 1961; Kilborn and Robson, 1965; Landon et al., 1965).

Though A.C.T.H. is known to be highly effective in the treatment of status asthmaticus and may be life-saving in the very ill patient (Segal and Herschfus, 1951; Ball, 1954; Johnson, 1954; Pearson, 1959; Sherman, 1963; Williams, 1963), the failure of adrenal response to A.C.T.H. demonstrated in some of the patients studied shows the possible danger of its use in patients receiving long-term steroid treatment. At the time of study adrenal failure was not suspected and the results of plasma 17-OHCS were not available. Severe respiratory distress due to asthma was the dominant clinical feature, and transient loss of consciousness similar to that observed in Case 3 may be seen during severe attacks of status asthmaticus in patients who have not received steroids.

A study of the progress in hospital of the three patients with adrenal suppression revealed that the asthmatic attacks were not adequately controlled with A.C.T.H. This failure to induce a satisfactory clinical response to treatment is also indicated by the amount of A.C.T.H. given in comparison with that given to the rest of the patients. These patients (and Case 4, who had a diminished and delayed plasma 17-OHCS response to A.C.T.H.) received A.C.T.H. infusions for periods ranging from 16 to 40 hours followed by injections of A.C.T.H.-gel 40 units every four hours for several days. Severe stress occurs during status asthmaticus, and the need for giving such patients adrenal steroids rather than A.C.T.H. is evident. During a subsequent admission to hospital the clinical response to hydrocortisone administration in Case 2 was prompt. The plasma 17-OHCS values, determined every hour during the A.C.T.H. infusion given immediately before hydrocortisone, revealed that adrenal failure was present.

The satisfactory plasma 17-OHCS response to A.C.T.H. recorded in 11 patients, despite previous treatment with continuous steroids for periods up to seven years, is in agreement with earlier reports on steroid-treated patients (Fredell et al., 1955; Larzelere et al., 1957; Carreon et al., 1960; Anderson and Kierulf, 1961; Robinson et al., 1962; Savage et al., 1962; Brinck-Johnsen et al., 1963; Treadwell et al., 1963). In these reports normal increase in urinary or plasma 17-OHCS was recorded during stimulation with A.C.T.H. in all the patients studied.

It is unlikely that the standard measurements employed in this study for treatment of the asthmatic attacks were responsible for the high plasma 17-OHCS values recorded in five of the patients before the administration of A.C.T.H. Intravenous aminophylline is not known to cause an increase in hydrocortisone secretion, and though injections of adrenaline may produce an eosinopenia, no increase in plasma 17-OHCS has been recorded (Sandberg et al., 1953; Ely et al., 1954; Hunter et al., 1955; Tyler et al., 1955). Exogenous adrenal steroids could not have contributed to the high basal plasma 17-OHCS values, since in four of these five patients the last dose of steroids was taken some 12 to 24 hours previously. The increased plasma 17-OHCS concentration in these patients may be attributed, at least in part, to the stress of status asthmaticus, and the further increase in plasma 17-OHCS recorded during stimulation with A.C.T.H. indicates that the adrenal glands had not been maximally stimulated. These five patients, however, did not appear clinically to be more distressed than those in whom plasma 17-OHCS values were within the normal range. Extra-adrenal factors may play a part, and these aspects are being investigated.

Summary

The plasma 17-OHCS response to A.C.T.H. (corticotrophin) was studied during attacks of status asthmaticus in 17 patients who had received long-term continuous steroid therapy.

Adrenal response to A.C.T.H. was normal or increased in 11 patients and diminished in three.

Three patients had severe adrenal suppression despite adequate A.C.T.H. treatment for three days. In one of these patients adrenal failure was again found during a subsequent attack of status asthmaticus. The progress of these patients in hospital is detailed.

In patients receiving long-term steroid therapy the possible danger of treating status asthmaticus with A.C.T.H. alone is emphasized.

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Medical Vagotomy: An Assessment

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Attempts have been made to predict the secretion of gastric acid after surgical vagotomy with a drainage procedure, by blocking the vagus nerves with atropine and hexamethonium or with propantheline in preoperative tests (McArthur, Tankel, and Kay, 1960; Gillespie and Kay, 1961; Checketts, Gillespie, and Kay 1966). These workers carried out two tests on their subjects before operation: the first was an augmented histamine test (Kay, 1953); in the second hexamethonium bromide 50 mg. and atropine 0.325 mg., or propantheline 30 mg., were given before the injection of histamine. If this drug-induced or "medical" vagal blockade in the second test brought about a large decrease in the response to histamine a similar large reduction in secretion was to be expected after surgical section of the vagi. On the other hand, in some patients the response to histamine was reduced by only a small amount (<35%) after medical vagotomy, and some of these subjects also had a small reduction in secretion after surgical vagotomy. It was suggested that a minority of patients with duodenal ulcer had "antral dominance" over the production of gastric acid, the vagi playing a lesser part; that it might be possible to pick them out before operation by the "medical vagotomy" test; and that they would be better treated by vagotomy and antrectomy than by vagotomy and drainage alone.

Our study is a critical examination of the above hypothesis, designed to answer the following questions: (1) Do the drugs block the vagi completely, as complete surgical vagotomy does? Does the "medical" block withstand the challenge of insulin-induced hypoglycaemia? (2) Does "medical" vagotomy provide a good forecast, for the individual patient, of the acid output he will have after complete surgical vagotomy? (3) If the forecast is accurate, what is its value?

Method

Instead of two preoperative tests, one with and one without medical vagotomy, we have used a single histamine-infusion test (Lawrie, Smith, and Forrest, 1964), injecting atropine and hexamethonium when maximal levels of secretion have been attained after 90 to 105 minutes. The subjects were male patients with duodenal or gastric ulceration, hiatus hernia, dyspepsia without any abnormality on barium-meal examination, and normal individuals. After an overnight fast a 16 F.G. duodenal tube with a metal tip was passed transnasally into the stomach, the contents of which were aspirated by continuous suction with an electric motor. The antihistamine mepyramine maleate (Anhistan) was given in a dose of 50–100 mg. intramuscularly at the start of the test. The histamine infusion was then set up, with either a paediatric drip set or a constant-infusion pump, to deliver 0.4 μg of histamine acid phosphate per kg. per minute intravenously throughout the test. The gastric secretion was aspirated by continuous suction, and separate samples representing 15-minute periods were collected.

After 90 to 105 minutes, when a steady rate of gastric secretion had been achieved, the medical vagotomy injection was given. Atropine sulphate 1.5 mg. (1/50 gr.) and hexamethonium bromide (C₉) 50 mg. were given together intramuscularly. Gastric secretion was then collected for a further two hours (in 74 tests) or four hours (28 tests). The "maximal" acid secretion was taken as the mean of the two or three 15-minute collections immediately before the injection of atropine and hexamethonium, while "acid output after medical vagotomy" was taken as the mean of the two or three lowest consecutive readings, which were usually recorded near the end of the test. The acidity of the samples was estimated by titration with N/100 NaOH, phenolphthalein being used as indicator.

Thirty-six men with duodenal ulcer underwent the above test, which lasted five to five and a half hours in 21 and three and a half hours in 15. They were then treated by vagotomy and pyloroplasty. Postoperative insulin tests (Hollander, 1948) showed the vagotomy to be complete. Seven to 14 days after operation a histamine-infusion test combined with medical vagotomy was carried out, identical in terms of drug dosage to the preoperative test, but in all cases the test ended two hours after the administration of the medical vagotomy injection, so that its total duration was about three and three-quarter hours.

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