EFFECT OF HALOTHANE AND METHOXYFLURANE ANAESTHESIA ON PLASMA CORTISOL CONCENTRATION IN RELATION TO MAJOR SURGERY*

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THE ANAESTHETIST frequently encounters severely debilitated patients who may be chronically ill and must undergo extensive operations, such as aortic graft for abdominal aortic aneurysm, excision of malignant lesions of the kidney, stomach, bowel, or generative organs, and radical neck dissection for malignancy involving the upper airway and oesophagus.

Despite deliberate and skilful care during induction and maintenance of anaesthesia, some of these patients develop progressive circulatory difficulties that do not respond adequately to lightening anaesthesia and administration of supportive fluids and blood. They may also respond poorly to more drastic measures of questionable efficacy, such as administration of digitalis preparations, vasopressors, and use of the head-low position.

The wary clinician can often predict that difficulties are likely to occur in such patients, particularly when there is weight loss, dry loose skin, evidence of deficient blood volume, chronic cardiopulmonary disease, lassitude, and complaints of general debility. On the other hand, there may not be such obvious indications, yet the patient seems incapable of responding to major stress.[1]

Although, under ordinary circumstances, prolonged stress rarely exhausts the capacity of the adrenal glands to secrete cortical hormones, the type of patient cited above may suffer from latent adrenocortical insufficiency which is usually due to previous non-specific therapy with cortical hormones; occasionally, however, adrenocortical insufficiency may exist without a historical reason. If cortical secretion does not rise in response to stress, circulatory homeostasis is lost and the patient may die in peripheral circulatory failure.

It has been shown that the ability of the body to respond to severe stress in a protective manner may be predicted by the adrenal cortical response to administration of adrenocorticotrophic hormone (ACTH)[2] and several other tests listed in Figure 1. A few clinics have used the ACTH test in selected cases to determine the diagnosis of adrenal cortical insufficiency, or to determine whether a patient is likely to have an adequate cortical response to a severe stressing situation such as major surgery.[3] This test has not been applied routinely for two reasons: adverse reactions to the parenteral administration of ACTH occur occasionally even with highly purified material, and the laboratory assay of blood and urinary cortisol has been a complicated and time-consuming procedure.

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EOSINOPHIL COUNT ↓

ALTERATION IN URINARY $^{Na}/_{K}$ RATIO

ACTH ⇩ measure urinary steroids
measure plasma 17 OH corticoids ↑

STRESS TESTS ⇩ measure plasma 17 OH corticoids ↑
Pyrogen; Hypoglycaemia
metopirone; Lysine - Vasopressin (LVP)

CORTROSYN TEST ⇩ measure plasma cortisol ↑

FIGURE 1. Tests of adrenal cortical response.

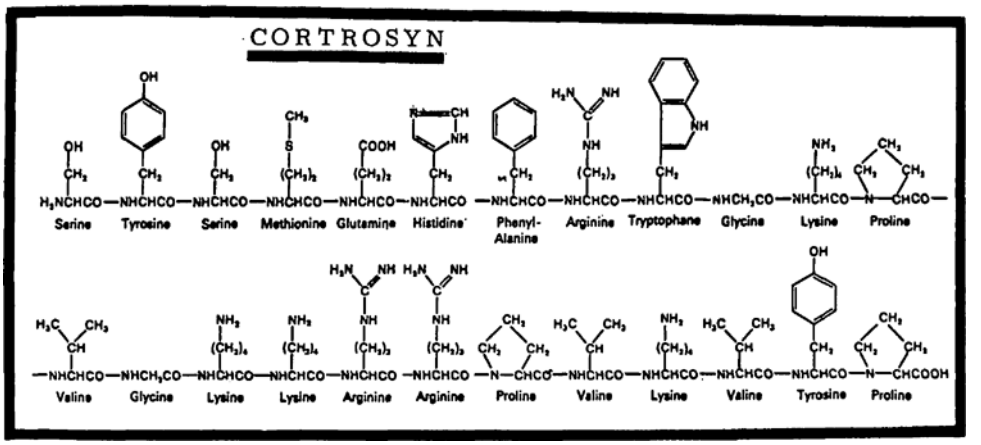

FIGURE 2. Structural formula of β 1-24 corticotropin (Cortrosyn, Synacthen).

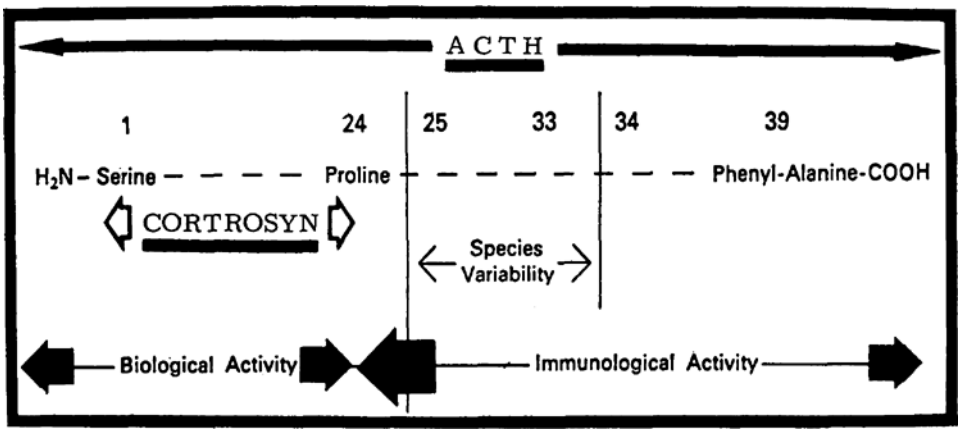

FIGURE 3. Schematic outline showing primary actions of ACTH and cortrosyn.

Simple fluorimetric techniques have now been developed which allow plasma cortisol measurements to be made rapidly, easily, and accurately. The reserve capacity of the "pituitary-adrenal axis" can be tested with a pure synthetic polypeptide, β 1-24 corticotropin (Fig. 2), known as Synacthen® (Cortrosyn® in the United States). This new material has the cortical-stimulating activity of ACTH and provides a reproducible stress response. Adverse reactions are unlikely because it does not contain the total chemical configuration which characterizes the immunological activity of ACTH (Fig. 3).

This study was undertaken particularly to determine whether debilitated elderly patients with clinical signs that might indicate adrenal cortical insufficiency respond normally to the administration of β 1-24 corticotropin, and to determine whether either halothane or methoxyflurane influences the adrenocortical response to surgical stress. The selection of case material was confined to patients who required prolonged major vascular surgery in order to have a uniform type of severe stress.

Materials and Methods

Patients in whom extensive vascular surgery was contemplated, and who appeared debilitated, were selected from the elective surgical schedule. Informed signed consent was obtained from each patient allowing us to perform the measurement of blood cortisol concentrations and the administration of the synthetic β 1-24 corticotropin on the day before and the day after operation as well as during the operation.

The test was carried out as follows: 6 ml. of venous blood was drawn into a heparinized syringe and placed in a blood tube. Then, lyophilized synthetic β 1-24 corticotropin, which was supplied in vials containing 0.25 mg. of the powder, was reconstituted with 1 ml. of saline and injected intramuscularly. Venous blood samples were drawn again exactly 30, 60, and 120 minutes after the injection of β 1-24 corticotropin. As a precaution, each time the test was done on a patient, a resuscitation kit was kept immediately at hand containing an Ambu-bag, epinephrine, and methylprednisolone, ready for use in case an acute hypersensitivity reaction occurred.

The plasma cortisol concentration was analysed in duplicate with each blood sample by the method of Mattingly.[4] This is a simple fluorimetric procedure for measuring free 11-hydroxycorticoids in human plasma. The blood sample is obtained by venipuncture using heparin as an anticoagulant, as noted above. Provided the blood is refrigerated immediately, it is not necessary to separate the plasma for up to 12 hours, and separated plasma may be kept much longer. Only 2 ml. of plasma are required for duplicate estimations, and the fluorescence can be read in a standard direct-reading fluorimeter. The procedure is relatively rapid in that six estimations can be completed in 90 minutes. This procedure has the added advantage of not being dependent on the accurate collection of 24-hour urine samples, and has been demonstrated to provide relatively accurate data.[5]

The criteria for a normal response in adult patients is as follows: The initial cortisol level should exceed 5 μg./dl. if the patient has not received a gluco-

corticoid within 12 hours; it should rise more than 7 μg./dl. in 30 minutes after injection of 0.25 mg. of β 1-24 corticotropin and should exceed 18 μg./dl. at this time regardless of the initial level.

Serial assays were done on 37 patients who received halothane anaesthesia and on 27 patients who received methoxyflurane anaesthesia. Four patients who had a previous history of therapy with corticoids were studied separately. In each case, the patient was premedicated with atropine approximately one hour beforehand. Most patients also received a modest dose of meperidine at the same time. Anaesthesia was induced with gallamine and a sleep dose of thiopentone and, after full oxygenation and endotracheal intubation, the patient's airway was connected to a mechanical respirator set at a rate of 14 to 18/min., and a tidal volume that was judged sufficient to maintain blood gases in the normal range. Anaesthesia was then maintained with halothane <2 per cent and nitrous oxide–oxygen (60:40) or methoxyflurane <1.5 per cent and nitrous oxide–oxygen (60:40). Balanced salt solutions, blood transfusions and other supportive therapy was administered as required. Thirty-two patients were 60 to 83 years of age and the remaining 36 patients varied in age from 24 to 59.

When the tests were performed on the day of surgery, the control sample was drawn immediately before induction of anaesthesia. In each case, the surgical incision coincided approximately in time with drawing of the 30-minute blood sample. The actual surgical procedure in all the reported cases exceeded 90 minutes. In 29 of the 37 patients who received halothane anaesthesia and in 19 of 27 patients who received methoxyflurane anaesthesia, instead of administering β 1-24 corticotropin, saline was injected intramuscularly (a "blank" test), while the remaining eight patients in each group were tested in the regular way. The purpose of using the "blank" test was to determine whether anaesthesia and surgical stress produce a rise in the plasma cortisol level equivalent to that which may be caused by the administration of β 1-24 corticotropin, and to determine in those patients who received the regular test during anaesthesia and surgical stress whether there is a synergistic or antagonistic response.

The data from all the tests were analysed statistically to determine whether variations in the plasma cortisol levels were significantly related to each of the circumstances under study.

Results

Over 150 tests of the response to β 1-24 corticotropin were carried out in this study in 68 patients, and in no case did an adverse reaction to the test drug appear. Analysis of duplicate estimations of plasma cortisol levels showed a mean difference of 1.0 ± 1.1 per cent, indicating that the laboratory test performance was highly reproducible.

Halothane (Tables I and II and Fig. 4)

In 29 patients who received a "blank" test during anaesthesia and surgery, the test on the day before showed an approximate doubling of the plasma cortisol level in response to β 1-24 corticotropin. In no case did the substantial rise fail to occur. The day after anaesthesia and surgery, the same test showed an initial

TABLE I

PLASMA CORTISOL LEVELS (μg./dl.) IN 29 PATIENTS WHO RECEIVED HALOTHANE ANAESTHESIA

	Control	30 min.	60 min.	120 min.
Day before	26.8	55.7	59.9	49.0
s.d. ±	7.9	12	15	15
s.e.m. ±	1.5	2.3	2.8	2.8
% diff.		+108	+123	+83
During anaesthesia*	26.0	30.8	37.1	47.0
s.d. ±	12	14	19	17
s.e.m. ±	2.3	2.7	3.6	3.2
% diff.		+19	+43	+81
Day after	43.5	71.8	80.0	70.6
s.d. ±	27	25	21	30
s.e.m. ±	5.1	4.7	4.0	5.7
% diff.		+65	+84	+62

*No 1-24 corticotropin given.

TABLE II

PLASMA CORTISOL LEVELS (μg./dl.) IN 8 PATIENTS WHO RECEIVED HALOTHANE ANAESTHESIA

	Control	30 min.	60 min.	120 min.
Day before	23.2	53.6	63.1	54.6
s.d. ±	9.3	6.7	8.7	20
s.e.m. ±	3.8	2.7	3.6	8.2
% diff.		+130	+172	+135
During anaesthesia*	26.8	46.4	57.7	62.7
s.d. ±	10	10	12	9.5
s.e.m. ±	4.1	4.1	4.9	3.9
% diff.		+73	+115	+134
Day after	43.9	75.6	78.8	72.0
s.d. ±	23	15	16	24
s.e.m. ±	9.4	6.1	6.5	9.8
% diff.		+72	+79	+64

*1–24 corticotrophin given.

much higher level of plasma cortisol. The response to β 1-24 corticotropin was quantitatively the same as occurred preoperatively. During anaesthesia and surgery *without* the administration of the synthetic preparation (a "blank" test), the plasma cortisol rose more slowly and to a lesser peak in response to the surgical trauma.

In eight patients in whom the synthetic preparation was given just preceding induction of anaesthesia, the rise again progressed during the surgical trauma, but reached a higher level than in those who received a "blank" test. Again, the postoperative levels were much higher initially and rose quantitatively by the same amount in response to the chemical stimulus. It appeared in these patients as if the administration of halothane anaesthesia might have suppressed the plasma cortisol response to the stress of anaesthesia and surgery and the administration of β 1-24 corticotropin, but this effect apparently did not persist, as indicated by the normal responses observed the day after operation.

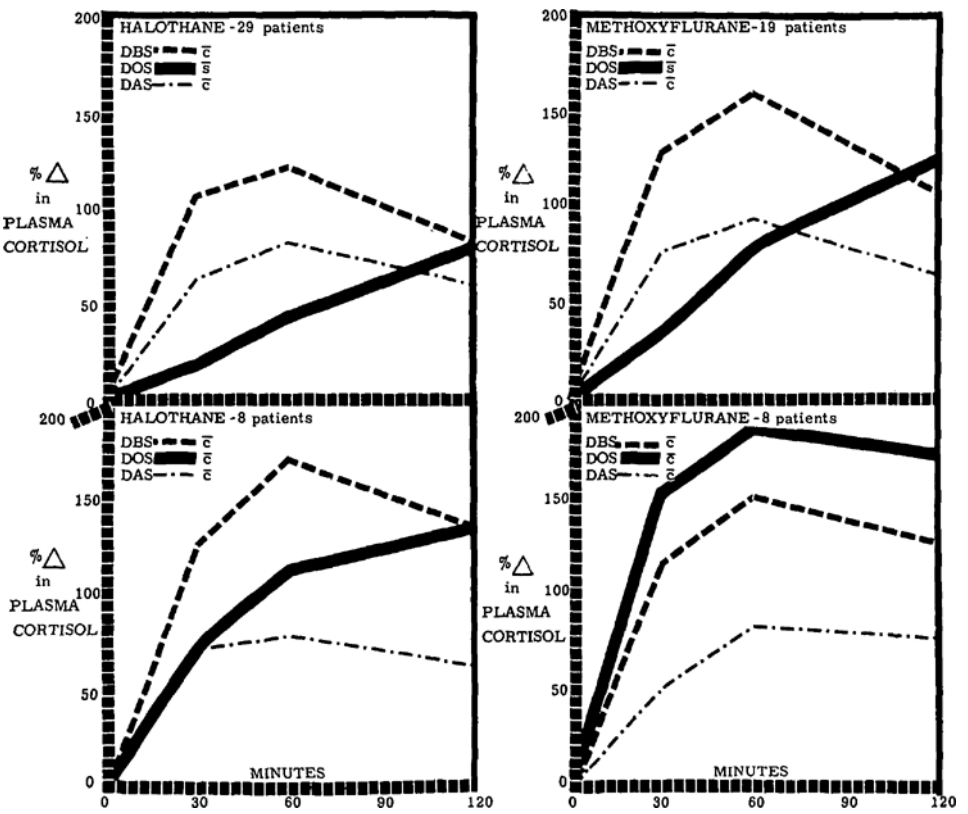

FIGURE 4. Per cent elevations in plasma cortisol levels. DBS = day before surgery; DOS = day of surgery; DAS = day after surgery.

Methoxyflurane (Tables III and IV and Fig. 4)

In 19 patients who received a "blank" test during anaesthesia and surgery, the test on the day before and after surgery was similar to that seen in the halothane group. During surgery, the response in the methoxyflurane group was again progressive but was appreciably greater than occurred in the halothane group.

In eight patients who received β 1-24 corticotropin just preceding induction with methoxyflurane anaesthesia, the response was much greater than occurred in the halothane group.

Review of Statistical Evaluation of the Data

Statistical analysis of the data with respect to the day of surgery may be summarized as follows: the measurement of the plasma cortisol level at the time of injection of β 1-24 corticotropin (zero time or control level) showed no significant difference between *any* of the patients. Statistically, all values came from the same population and premedication had no effect.

The measurements of the plasma cortisol level thirty minutes after the injection of β 1-24 corticotropin showed the most striking differences between the groups. In the patients who received halothane anaesthesia, the administration of β 1-24

TABLE III

PLASMA CORTISOL LEVELS (μg./dl.) IN 19 PATIENTS WHO RECEIVED METHOXYFLURANE ANAESTHESIA

	Control	30 min.	60 min.	120 min.
Day before	23.9	55.4	62.5	49.6
s.d. ±	8.1	11	14	21
s.e.m. ±	2.0	2.7	3.4	5.1
% diff.		+132	+161	+107
During anaesthesia*	25.7	33.3	45.9	57.3
s.d. ±	8.5	17	22	22
s.e.m. ±	2.1	4.1	5.3	5.3
% diff.		+30	+79	+124
Day after	42.6	75.7	83.7	70.8
s.d. ±	13	13	17	23
s.e.m. ±	3.1	3.1	4.1	5.6
% diff.		+78	+96	+66

*No 1–24 corticotrophin given.

TABLE IV

PLASMA CORTISOL LEVELS (μg./dl.) IN 8 PATIENTS WHO RECEIVED METHOXYFLURANE ANAESTHESIA

	Control	30 min.	60 min.	120 min.
Day before	22.5	48.9	56.4	50.9
s.d. ±	9.3	14	18	28
s.e.m. ±	3.5	5.3	6.8	11
% diff.		+117	+151	+126
During anaesthesia*	20.8	53.1	59.9	56.9
s.d. ±	9.1	18	21	26
s.e.m. ±	3.4	6.8	7.9	9.3
% diff.		+155	+188	+173
Day after	46.0	69.7	84.7	81.4
s.d. ±	6.3	13	19	32
s.e.m. ±	2.4	4.9	7.2	12
% diff.		+52	+84	+77

*1–24 corticotrophin given.

corticotropin elevated the plasma cortisol level only somewhat above the "blank" level; the difference (Student's *t*-test) was probably significant ($p = 0.05$). However, in the patients who received methoxyflurane anaesthesia, the injection of β 1-24 corticotropin showed a much greater plasma cortisol level that was highly significant ($0.01 > p > 0.001$). The patients who did not receive β 1-24 corticotropin on the day of anaesthesia showed no statistically significant difference and could be taken as a common group. One may conclude that halothane anaesthesia suppresses the response to β 1-24 corticotropin when compared to the effect of methoxyflurane, and that 30 minutes of anaesthesia with either of these agents does not cause an appreciable rise in the plasma cortisol level without exogenous stimulation.

After 60 minutes, and 120 minutes when the effect of surgical trauma becomes the dominant factor, the differences between the two anaesthetics in response to β 1-24 corticotropin decreased. However, the elevation of plasma cortisol was

TABLE V

RISE IN PLASMA CORTISOL (μg./dl.) VALUES AFTER β 1-24 CORTICOTROPIN IN PATIENTS WHO WERE ON STEROID THERAPY*

Patient	Control	30 min.	60 min.	120 min.
1	29.5	73.4	59.8	34.0
2	16.3	22.0	24.0	27.0
3	14.8	37.7	45.5	46.5
4	4.0	44.0	50.0	45.5

*Preoperative plasma cortisol assays in μg./dl. in four patients with a history of corticosteroid therapy. Note that the first patient had normal values; patient 2 had a low plasma cortisol concentration and a poor response to stimulation with β 1-24 corticotrophin; patients 3 and 4 each had a low plasma cortisol concentration, but both responded in the normal way to stimulation by β 1-24 corticotrophin.

markedly greater in these patients than in the ones who did not receive β 1-24 corticotropin ($0.01 > p > 0.001$). Although the latter patients who received methoxyflurane had a higher plasma cortisol level at 60 minutes and 120 minutes than those who received halothane, the differences at these two time intervals were not statistically significant ($p = 0.16$ and $p = 0.09$ respectively). One may conclude that the stress of surgery tends to annul any differences in the effect of the two anaesthetics.

Four patients were encountered who had a previous history of treatment with cortisone preparations (Table V). The first patient was a 61-year-old male who was in ASA physical state 3 on account of severe emphysema, asthma, and an elevated BUN. Asthma attacks had recently been treated with a cortisone preparation. The day before surgery, he was found to have a normal plasma cortisol level and he responded adequately to β 1-24 corticotropin. At surgery under halothane–nitrous oxide anaesthesia for 6½ hours, an abdominal aortic aneurysm was replaced with a bifurcation graft. The weighed blood loss was approximately 4300 ml. which was replaced with 4000 ml. of bank blood. During operation, the serial tests of plasma cortisol were made without administering β 1-24 corticotropin. A normal response occurred at surgery and again the following day, in response to the chemical stimulus. He had an uneventful recovery.

The second patient was a 30-year-old male who had been on steroid therapy five years for treatment of a haemolytic anaemia of unknown aetiology. He had a grossly enlarged liver and spleen and was on a downhill course following a recent bout of pneumonia. At the time he was scheduled for a splenectomy, he was under treatment with antibiotics and prednisone. The day before surgery, his haemoglobin was 9.8 gm. and haematocrit 30 per cent; the plasma cortisol was initially normal, but there was no appreciable response to β 1-24 corticotropin. Splenectomy was done under methoxyflurane–nitrous oxide–oxygen anaesthesia for two hours and 20 minutes. During the operation, weighed blood loss was approximately 1200 ml., which was replaced with 1000 ml. fresh whole blood. The plasma cortisol concentration fell slowly during the operation but remained within the normal range. Treatment with hydrocortisone was given from the day before until the day after surgery and was continued with prednisone. The plasma cortisol level was elevated the first postoperative day and responded moderately

to β 1-24 corticotropin. His recovery from the operation was relatively uneventful. On the sixth postoperative day, the plasma cortisol test showed further depression on account of steroid therapy and the test response again was attenuated.

The third patient had *not* received steroids for five years and had normal tests, and the fourth patient had a very low resting level of plasma cortisol (4 μg. %) following a short period of steroid therapy, but responded normally to the chemical stimulus.

There was no appreciable difference in the plasma cortisol levels or the response to β 1-24 corticotropin in the male and female patients and, in general, the elderly patients had similar levels and responses to the chemical stress and surgical procedure as younger patients.

Discussion

Synacthen® is β 1-24 corticotropin prepared synthetically. It is an open chain polypeptide containing the first 24 amino acids in sequence from the N-terminal. This configuration is common to all types of natural corticotropin. The empirical formula is $C_{136}H_{210}N_{40}O_{31}S$ with an approximate molecular weight of 2934.

Pharmacology

Synacthen retains the full range of corticosteroidogenic and other activities characteristic of natural ACTH which contains 39 amino acids.[6–17] Studies have shown that the biological activity of ACTH resides in the N-terminal portion of the molecule, whereas immunological activity resides in the C-terminal portion. These activities can be dissociated.[16]

Synthetic polypeptides of varying chain lengths have been studied, and it has been established that the N-terminal 20 amino acid residues constitute the smallest sequence which retains full *in vivo* adrenal stimulating activity.[13–16] Comparative clinical studies indicate that 0.25 mg. of β 1-24 corticotropin given as an intravenous infusion produces an adrenal effect equal to that of 25 units of natural ACTH.[7–10,12,15,17] Partial or complete loss of biological activity is noted with progressive shortening of the chain beyond 20 amino acid residues.

Animal, human, and synthetic 1-39 ACTH exhibit similar immunological activity. This activity resides in the C-terminal portion of the molecule, and the 22-39 amino acid residues exhibit the greatest degree of activity. In contrast, synthetic peptides with 1-19 or fewer amino acids have no detectable immunological activity. Those containing 1-23, 1-24, or 1-26 amino acids have very little immunological activity although they have full steroidogenic activity.[16] These properties of β 1-24 corticotropin assume added importance in view of the known antigenicity of natural ACTH preparations.[18–22]

Reported Clinical Studies

Synthetic β 1-24 corticotropin has been used primarily as a test for determining adrenal cortical function. The duration of effect is relatively short-lived when it is given intravenously or intramuscularly in non-depot form. Maximal response is noted at approximately 45 to 60 minutes with return to control plasma cortisol levels at the end of four hours. A number of dosage regimens have been described.

Karl[7] infused 0.25 mg. of β 1-24 corticotropin into 15 subjects over a six-hour period and noted increases in the secretion of 17 hydroxycorticosterone of the same order of magnitude as seen after infusing 25 units of natural ACTH. He also noted increased urinary excretions of the chief cortisol, corticosterone, and androgenic metabolites, and concluded that the synthetic material increases the adrenal cortical production of these to the same degree as natural ACTH in equivalent doses.

Jenny and associates[8] reported comparable increases in plasma 17 hydroxycorticosterone levels following intravenous infusions of 0.25 mg. of β 1-24 corticotropin and equivalent doses of natural ACTH in nine subjects. Urinary steroid excretion was also increased. Eosinophil counts dropped by 85 to 100 per cent in those subjects with normal adrenal function. These findings have been amply confirmed by others.[9,10,12,14,15,17]

Moncloa and associates[22] have described a one-hour intravenous ACTH test. Immediately following control blood sampling, 0.25 mg. of the synthetic material, dissolved in 5 ml. of saline, is slowly injected intravenously and another blood sample obtained one hour later. An approximately two-fold increase in plasma cortisol levels is indicative of normal adrenal cortical function. Patients with adrenal insufficiency or hyperplasia showed the expected responses.

Synthetic β 1-24 corticotropin has also been given intramuscularly. The duration of adrenal stimulation is shorter than that seen following injection of an equivalent amount of natural ACTH despite comparable plasma cortisol levels for the first hour. It is believed that this is a function of the longer amino acid sequence which delays the intravascular inactivation of the natural hormone.[9]

A number of investigators have shown that the synthetic material, given intramuscularly, is a rapid and safer test of adrenocortical function. In adults, for example, a single injection of 0.25 mg. was given and blood samples were drawn 30 minutes later for plasma cortisol level determinations.[9,11,21,22] An approximate doubling of resting plasma cortisol levels is indicative of a normal adrenal response. In infants less than two years of age, a dose of 0.125 mg. has been used and plasma 11-hydrocorticosterone levels were checked at 30 or 60 minutes.[23] A minimum of a three-fold increase in control levels was noted in this group at the end of 60 minutes.

Because synthetic β 1-24 corticotropin exhibits only slight immunologic activity and does not contain foreign animal protein, it is less risky to use than natural ACTH. Patients known to be sensitized to natural ACTH with markedly positive skin tests showed negative responses when tested intradermally with the synthetic preparation.[18] Further, a number of investigators have documented this greater margin of safety in patients suffering from hypersensitivity diseases such as asthma, or who have previously had an adverse reaction to natural ACTH.

Jenny and associates[8] treated three patients with acute asthma with single intravenous infusions of 0.25 mg. of β 1-24 corticotropin with "striking" responses in all. Two additional patients who had previously reacted to intravenous infusions of natural ACTH (one with urticaria, one with anaphylactic shock) received infusions of the synthetic preparation without incident. Landon *et al.*[9] report similar experiences with two patients previously sensitized to natural ACTH.

El-Shaboury[14] administered 0.5 mg. of β 1-24 corticotropin intravenously to five asthmatic patients hypersensitive to natural ACTH. One of these patients also received twice daily intramuscular injections of the same dose for an additional seven days. No ill effects were noted in any patient.

Zarate and Quinteros[19] administered a series of infusions (ranging from 1 to 22) of the synthetic material (0.25 mg.) to 13 patients suffering from various allergies. Eleven (three also sensitive to natural ACTH) were in status asthmaticus and two had severe forms of dermatitis. Ten (including two sensitive to ACTH) of the thirteen patients tolerated all infusions without incident. One patient displayed "psychic excitation" during each infusion, but this was not severe enough to stop treatment. The remaining two patients suffered allergic reactions, but in one instance this was not ascribed to the synthetic material. It would appear, therefore, that hypersensitivity reactions to the synthetic β 1-24 corticotropin are possible, at least in patients with existing allergies. Charpin *et al.* reported a hypersensitivity reaction in a patient previously sensitized to natural ACTH.[20]

Studies Related to Anaesthesia and Surgery

In studies of the adrenocortical responses using this test, the plasma cortisol concentration was shown to have a diurnal variation in the range of 10 to 25 μg./dl.[24] (Fig. 5). During psychic stress, as occurs preceding a surgical operation, the plasma cortisol level appears to be elevated to the upper level of the diurnal variation, particularly in patients with a high degree of discomfort involvement rather than psychic depression, and may be aggravated the longer the patient has to wait for the induction of anaesthesia.[25] The administration of premedicant drugs (atropine and meperidine) did not raise or lower the plasma cortisol. In

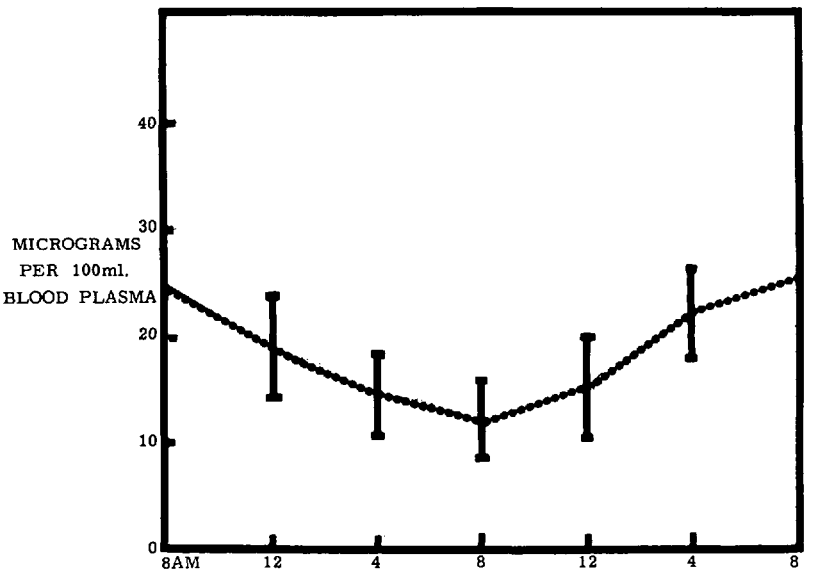

FIGURE 5. Diurnal variation in plasma cortisol levels (from Nilsson, Arner, and Hedner, ref. no. 24).

one report, haloperidol and phenoperidine appeared to cause a rise,[24] and in two recent reports from one centre[26,27] describing measurements of 17 hydroxycorticosteroids, premedication with pentobarbital (50 to 100 mg. orally), meperidine (35 to 70 mg. i.m.) and atropine (0.5 mg. i.m.), in 20 patients there was no change observed[26] and in 11 patients there was a slight reduction.[27] If all of the cases in the second study were done during the morning hours (as is very likely), the lowering observed in the 17 hydroxycorticoids probably reflects merely the diurnal changes.

During the course of a surgical operation, the level rises gradually to approximately twice the resting level and usually remains elevated to a substantial degree beyond 12 hours after a major surgical procedure. The rate at which the elevation develops and the height of the peak attained is believed to depend upon the increased rate of production of cortisol by the adrenal cortex, the rate of conjugation of cortisol by the liver, and the rate of utilization by other tissues. Surgical complications such as secondary haemorrhage or infection, fever, and pain prolong the increased output. It appears that even in severely debilitated and elderly patients the capacity of the adrenal cortex to secrete cortisol at a high rate during prolonged surgical stress is considerable, and exhaustion is an exceptional occurrence unless the patient has shown preceding evidence of severe adrenal insufficiency or has quite recently received therapy with corticosteroid preparations.[3,24]

Effect of Halothane and Methoxyflurane Anaesthesia and Surgery

With the technique described in this paper, it has been possible to infer the rate of production of cortisol from analysis of peripheral venous blood samples. The adrenal cortex can increase cortisol production by as much as ten times the resting level during the course of chemical stimulation or during the acute severe stress of a surgical operation. Methoxyflurane anaesthesia does not seem to attenuate this response, whereas our limited data appear to show that halothane anaesthesia may reduce the development of a marked elevation in the plasma cortisol. It appears from this study that halothane depresses the release of ACTH from the anterior pituitary or blocks its effect. However, at this stage it is not possible to say whether the effect of halothane may also be due to a reduction in the stress response, a reduction of the stress itself, or changes in the rate of conjugation or utilization of plasma cortisol. It is apparent from other work that metabolic derangements due to halothane anaesthesia are also minimal.[28] In the study by Nilsson and associates,[24] it was also reported that halothane–nitrous oxide (as well as diethyl ether–nitrous oxide) appeared to suppress the adrenal cortical response to stress whereas during anaesthesia employing the neuroleptanalgesic drugs it was not suppressed, as we observed with methoxyflurane. However, their report also contained too few case studies to allow clear-cut evidence that these effects may be attributed to the anaesthetic agents in question. Previous reports by Virtue and associates[29] and Hammond and associates[30] agreed that diethyl ether causes a prompt and persistent significant rise in plasma corticosteroids, whereas thiopental and spinal anaesthesia do not have much effect and cyclopropane has an intermediate effect.

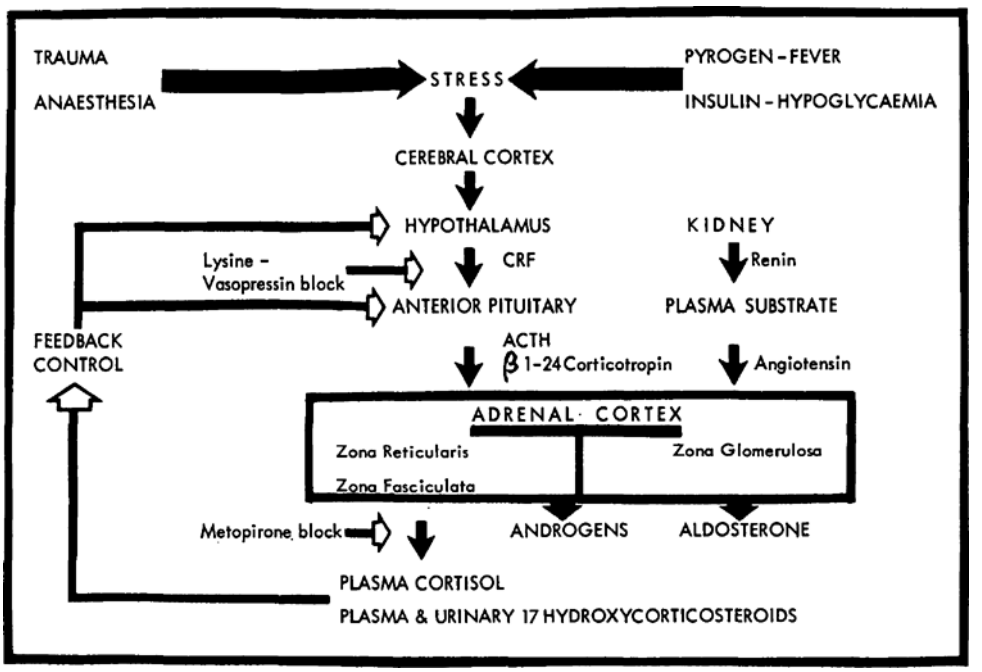

FIGURE 6. Schematic outline of factors influencing adrenocortical secretions.

In the Japanese papers cited above, when induction with thiopental was carried out in ten patients, the effect of halothane was shown not to be significant, whereas a rise to almost twice the control level in another ten patients occurred when no thiopental was used.[26] The effect of methoxyflurane was studied in 11 patients: during induction (without thiopental) there was no appreciable change until the effect of surgery was added; then the elevation exceeded twice the control level observed.[27] In a recent study of a new halogenated ether, the plasma cortisol levels rose in the normal way in every case.[31]

Significance of Plasma Cortisol Levels (Fig. 6)

The secretion of cortisol is stimulated by the action on the adrenal cortex of the hormone corticotrophin (ACTH), which originates from the anterior lobe of the pituitary. The release of ACTH, in turn, is triggered by a hormone of hypothalamic origin, corticotrophin releasing factor (CRF). Under basal conditions, the level of circulating cortisol is maintained within the range 10 to 25 μg./dl. plasma by means of a feedback mechanism by which a rise of plasma cortisol inhibits ACTH release, while a fall results in the increased secretion of this pituitary hormone. A second mechanism operates in response to a variety of stressful situations (trauma, infection, metabolic upsets, and surgery). This takes precedence over feedback control and provides a means for temporary elevation of plasma cortisol levels. This adrenal response to stress is of vital physiological importance, and adrenocortical insufficiency, whether due to hypothalamic, pituitary, or adrenal dysfunction, is frequently unsuspected until anaesthesia, surgery, or septicaemia precipitates an acute crisis. Severe dysfunction of the

pituitary adrenal axis is associated with subnormal levels of plasma cortisol, so it might seem that the determination of basal levels alone would enable adrenocortical insufficiency to be diagnosed by a single plasma cortisol estimation. Unfortunately, many patients with pituitary or adrenal dysfunction have basal values which lie within the normal range and can produce the quantity of steroid which is sufficient to meet small variations in the basal requirements, but develop insufficiency precipitously in stressful situations. Consequently, it is essential to employ dynamic tests which determine the functional integrity and the reserve capacity of the entire pituitary-adrenal axis. Hence, the criteria for a normal response to administration of β 1-24 corticotropin are essential to a valid interpretation of changes induced in the plasma cortisol level.[9,21]

Significance of Plasma Cortisol Alterations

Since there is no clear temporal relationship between metabolic changes *following* major surgery, such as changes in nitrogen balance, renal conservation of sodium, loss of potassium, and water retention, and the *concurrent* rise in plasma cortisol (and a rise in blood sugar), it is generally felt that the role of plasma cortisol in relation to the metabolic response is "permissive" rather than directly causative.[3] In acute medical stress, such as pneumonia, myocardial infarction, fatal poisoning, gram negative septicaemia, and unbalanced diabetes with ketosis, only in the latter severe metabolic upset is there consistent evidence of a significant rise in the plasma cortisol level.[32]

It appears as if the anaesthetics that may be followed by a significant rise in the blood sugar (e.g., diethyl ether, neuroleptanalgesics) are accompanied by a greater rise in adrenocortical secretions than is observed during spinal, thiopental, halothane, and methoxyflurane anaesthesia.[24,26,27,29-31] It has been suggested that different anaesthetics may act at different neural levels in their final effect on the hypothalamus and on ACTH release.[33,34] Some also feel that the adrenal cortex, through its secretion of cortisol, is the main defender of blood glucose homeostasis.[35]

Whatever the underlying mechanism of action may be, it appears certain to the clinician that, for a patient to survive an anaesthetic and a major surgical operation, a responsive adrenal cortex is virtually essential, unless exogenous adrenocortical steroids are administered, for, in its absence, irreversible circulatory collapse may develop. The specific mechanism by which plasma cortisol maintains the circulation during anaesthesia and surgery remains unknown.

Summary and Conclusions

Serial assays of plasma cortisol concentrations were carried out before, during, and after major surgical procedures in 68 patients, employing halothane and methoxyflurane as the primary anaesthetic agents. A simple fluorimetric assay procedure was used which provided accurate data rapidly.

Synacthen® (synthetic β 1-24 corticotropin) was employed in place of natural ACTH as a chemical stimulus of the adrenal cortex and was found to be an effective and safe test of the patients' response to stress. No immunological reactions occurred with this preparation.

Atropine and meperidine premedication did not affect the response to the test. The initial rise in the plasma cortisol levels after induction of anaesthesia was slower than that produced by the injection of β 1-24 corticotropin, probably due to the administration of thiopentone during induction of anaesthesia.

The plasma cortisol levels rose to quite high levels during surgical operations with methoxyflurane anaesthesia when synthetic β 1-24 corticotropin was administered, whereas they were somewhat depressed when halothane anaesthesia was employed. However, there was no striking difference between the two anaesthetics and surgery when no β 1-24 corticotropin was given.

The significance of the plasma cortisol level with respect to circulatory homeostasis is not known, but an adequate level appears to be essential during induction of anaesthesia and the performance of major surgery.

Elderly patients had the same general response on the plasma cortisol level during anaesthesia and surgery as younger patients, and there were no apparent differences due to the sex of the patient provided adrenocortical insufficiency was not present.

This test may be particularly useful in patients who have received steroid therapy in the past, in order to determine whether they require supportive therapy during an operation.

Résumé

Nous avons fait des recherches en série pour déterminer dans le plasma les concentrations en cortisol avant, pendant et après des opérations majeures chez 68 malades chez qui le principal agent anesthésique était ou l'halothane ou le méthoxyflurane. Nous avons fait un simple test fluorimétrique, test qui donne des résultats précis rapidement.

A la place de l'ACTH naturelle comme stimulant chimique du cortex surrénalien, nous avons utilisé la Cortrosyn® (corticotropine β 1-24 synthétique), produit qui s'est avéré efficace et de toute sécurité pour évaluer la réponse des malades à l'agression. Avec ce produit, nous n'avons observé aucune réaction immunologique.

La prémédication à la mépéridine et à l'atropine n'a pas modifié la réponse au test. L'élévation initiale dans le plasma des taux de cortisol après l'induction de l'anesthésie a été plus lente que celle produite par l'injection de β 1-24 corticotropine, probablement à cause de l'administration de thiopental au cours de l'induction de l'anesthésie.

Les taux de cortisol plasmatique ont atteint des niveaux plutôt élevés au cours des opérations faites sous anesthésie au méthoxyflurane lorsque nous injections de la β 1-24 corticotropine synthétique alors qu'ils étaient plutôt abaissés au cours de l'anesthésie à l'halothane. Toutefois, lorsque nous ne donnions pas de β 1-24 corticotropine, nous n'avons pas observé de différence marquée entre les deux agents anesthésiques et la chirurgie.

Nous ne connaissons pas la signification du taux de cortisol plasmatique en ce qui concerne l'homéostase circulatoire, mais, pour faire l'induction de l'anesthésie et pour pratiquer la chirurgie, il nous semble essentiel que le malade en ait un taux adéquat.

En général, les vieillards ont répondu de la même façon que les plus jeunes en ce qui concerne le taux de cortisol plasmatique au cours de l'anesthésie et de la chirurgie et, pourvu qu'il n'existe pas d'insuffisance surrénalienne, nous n'avons pas observé de différences entre les deux sexes.

Ce test peut être utile plus particulièrement chez des malades qui, dans le passé, ont reçu une thérapie aux stéroïdes pour déterminer s'ils ont besoin d'une thérapie de support au cours d'une opération.

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