Plasma Levels of ACTH and Cortisol in Man during Diethyl Ether Anesthesia and Surgery

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Levels of ACTH in the peripheral plasma of ten patients during ether anesthesia alone and during and after laparotomy were determined by a modification of Lipscomb and Nelson's bioassay method. Levels of free cortisol in the plasma were determined simultaneously. Results of pituitary-adrenocortical reserve tests of all patients in the preanesthetic period were within normal limits. Plasma ACTH levels were very low (estimated less than 1 mU./100 ml.). A remarkable increase of pituitary-adrenocortical activity was noted during anesthesia, which was induced and maintained with diethyl ether-nitrous oxide at a depth of plane 2–3 of stage III. During induction of anesthesia and during surgery large amounts of ACTH were released intermittently, with two or three steep peaks in the plasma levels. In contrast, the level of free cortisol in the plasma rose gradually. Our data indicate that the increased levels of free cortisol in the plasma were the result of increased plasma ACTH activity.

MUCH EVIDENCE has accumulated concerning the effects of anesthesia and surgical stress on adrenal cortical function.[1-6] Furthermore, an increase in plasma ACTH with surgical stress has been shown in man and in animal experiments.[7-11] However, ACTH levels in human plasma during anesthesia have not been reported previously. The present study was undertaken to evaluate the effects of anesthesia alone on the plasma ACTH concentrations of patients and to compare the results with the effects of anesthesia plus surgery. We attempted to explore the quantitative relationship between plasma ACTH levels and the degree of adrenocortical activity as judged from simultaneous measurements of free cortisol in the plasma.

Method

Nine male patients and one female patient, ranging in age from 31 to 56 years, were the subjects of the study. All patients underwent elective gastrectomy for cancer or gastric or duodenal ulcer, except one patient who underwent cholecystectomy for cholecystitis. No patient had hepatic, renal, or endocrinologic disease, or a history of receiving steroid therapy. Preoperatively each had both an adrenocortical reserve test and a pituitary reserve test. The former test was done with an intramuscular injection of ACTH-Z 40 units; normally, there is a three- to fivefold increase in 24-hour urinary 17-hydroxycorticosteroids.[13] The latter test was performed with orally given Metyrapone in a dose of 750 mg. every four hours (total 3 Gm.); normal subjects show a twofold increase or more in 24-hour urinary 17-hydroxycorticosteroids.[14] Urinary 17-hydroxycorticosteroid determinations were made according to the method of Peterson *et al.*[15] All results were within normal limits.

The ten patients received pentobarbital (nembutal), 100 mg., by mouth one and a half hours before operation, and meperidine (demerol), 35 mg., and atropine, 0.5 mg., intramuscularly one hour before operation. Anesthesia was induced with nitrous oxide 2 l/min. and oxygen 2 l/min.; ether was given with a wick-type vaporizer. After 15 to 20 minutes of anesthesia, endotracheal intubation was done without use of a muscle relax-

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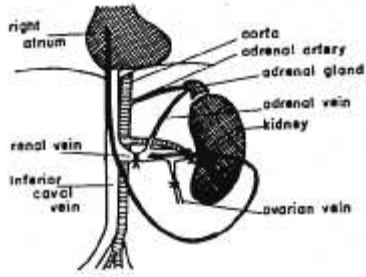

FIG. 1. Method of cannulation in the rat for biologic assay of human plasma ACTH.

ant. For maintenance of anesthesia, the depth was kept at plane 2–3 of the third stage as judged by Guedel's signs.[12] Respiration was assisted intermittently throughout the procedure. The operations lasted for an hour and 40 minutes to 3 hours and 50 minutes. The duration of anesthesia ranged from two hours and 30 minutes to four hours and 40 minutes.

Ten to 12 plasma samples were obtained from each patient: 1) in the morning at 8:30, ten minutes before induction of anesthesia; 2) every ten minutes during anesthesia, for at least 30 minutes; 3) every 30 minutes from the start of surgery to a half hour after the end of the operation. Blood was transfused to replace the loss due to sampling and operation. Thirty ml. of venous blood were drawn through an 18-gauge needle into a syringe previously rinsed with heparin. The plasma was separated within 30 minutes in a refrigerated centrifuge, then frozen at −20° C. for storage, and thawed within one month, prior to bioassay.

The plasma was assayed for ACTH using the adrenal venous corticosterone (compound B) method in hypophysectomized rats according to Arimura's[16] modification of the method of Lipscomb and Nelson.[17, 18] Female albino rats of the Wistar strain, weighing from 140 to 190 Gm., hypophysectomized two hours previously, were used. The details of the technique were as follows: the left renal vein was ligated at the junction with the inferior caval vein and the portal region of the kidney to secure adrenal venous blood through a polyethylene catheter. Adrenal venous blood was collected for ten minutes; ten minutes later 2 ml. of the patient's plasma were injected into the vena cava over a period of two minutes. The catheters placed in the adrenal vein and the inferior vena cava were connected and the blood was allowed to re-circulate. Fifteen minutes after the beginning of injection of the sample, the second adrenal venous sample was collected (fig. 1).

Assay for corticosterone in rat plasma was made with a Farrand fluorometer by the sulfuric acid fluorescence method of Guillemine *et al.*[19] The increase in adrenal venous corticosterone secretion rate per minute after the injection of the test plasma was used as an index of ACTH activity in the sample tested. Using USP Reference Standard corticotropin, linearity of response to log dose was obtained over a range from 0.02 to 0.32 mU. (milliunit) of ACTH, with a precision index of 0.32, using five rats at each dose (fig. 2). Assay for free cortisol in plasma was carried out by the method of Peterson *et al.*[20] The values for

Amount of ACTH	Number of Rats	Response Mean ± St.E.	Index of Precision
Saline	7	−2 ± 5.6	
0.02 mU	7	29 ± 9.2	
0.04 mU	7	95 ± 21.1	0.319
0.08 mU	7	171 ± 24.9	
0.16 mU	7	240 ± 27.6	
0.32 mU	7	308 ± 49.2	

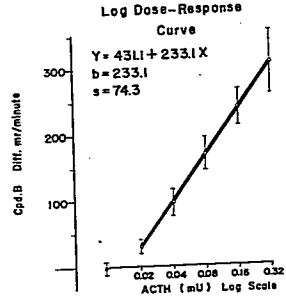

FIG. 2. ACTH U.S.P., dose–response in terms of increase in adrenal venous compound B (= corticosterone) secretion rate (mr./min.) in the rat.

TABLE 1. Effects of Ether Anesthesia and Surgery on Plasma ACTH Levels (milliunit per 100 ml. = mU/dl.) in Ten Patients

Cases	Time (minutes)										
	Pre. Ind.	Anes. 10	20	30	Op. 5	30	60	90	120	Op. End	30
1	N.D.	N.D.	1.5	0.7	—	1.5	N.D.	0.8	—	1.3	—
2	N.D.	N.D.	2.0	—	2.7	1.6	N.D.	1.4	0.8	0.8	—
3	N.D.	0.8	0.8	—	3.2	0.7	2.5	1.9	1.5	3.2	2.6
4	N.D.	—	17.1	2.7	1.7	3.0	6.5	1.5	2.5	1.3	1.3
5	N.D.	—	0.9	0.8	2.4	N.D.	N.D.	N.D.	N.D.	—	0.8
6	0.8	1.2	N.D.	—	—	0.8	N.D.	1.3	2.0	—	2.6
7	N.D.	N.D.	N.D.	0.8	—	N.D.	4.0	1.7	—	—	N.D.
8	N.D.	N.D.	0.8	1.3	—	N.D.	1.6	N.D.	1.4	1.3	0.8
9	N.D.	N.D.	3.4	—	2.6	N.D.	6.6	2.6	—	—	1.5
10	N.D.	N.D.	N.D.	0.8	N.D.	—	3.1	1.4	N.D.	—	1.3

N.D. = Non-detectable.

each point in the table 1 represent the corticosteroid responses of at least two rats.

Results

Effects of preanesthetic medication on plasma ACTH activity were nondetectable, that is, less than 1 mU. ACTH concentrations in the plasma during induction of ether anesthesia demonstrated transient but remarkable increases (table 1). The values ranged from 0.8 to 2.0 mU./100 ml. (= dl.), except in one case where a value of 17.0 mU./dl. was observed. The plasma ACTH concentration decreased abruptly in the latter in a short time. Although some patients showed no change, in most the plasma ACTH level reached a second high peak one hour after the induction of anesthesia, ranging from 0.8 to 3.2 mU./dl. A third peak of plasma ACTH concentration was detected later in some patients. In other words, two or three steep peaks were observed in plasma ACTH levels during anesthesia and surgical operation.

The mean cortisol concentration at 8:30, after administration of preanesthetic medication, was 14.4 μg./100 ml. (range 8–19 μg.). During the first ten minutes of diethyl ether anesthesia, it fell slightly to 13.0 μg./100 ml. (range 7–17 μg.), but increased to an average of 20.2 μg./100 ml. (range 14–29 μg.) during the second ten minutes after the start of operation, and continued to rise for 30 minutes after the end of operation (table 2). The stepwise elevation of free cortisol in plasma coincided with increases of plasma ACTH concentrations in six of ten patients.

Discussion

The present findings are in agreement with those of others that the concentration of ACTH in the plasma of unstressed subjects is below 1 mU. (milliunit)/100 ml.[7, 10, 11, 17] For instance, Cooper and Nelson,[7] without mentioning premedication, found in 10 patients a mean preoperative ACTH level in plasma of 0.6 mU./100 ml. on the morning before operation. In our experiment, the level of plasma ACTH was distinctly elevated to 0.8–3.4 mU. in seven patients after 20 minutes of ether anesthesia alone, and was not detectable in the remaining three patients. The ACTH level again was increased markedly (1.7–3.2 mU.) within five minutes of the start of operation; then it decreased, and again rose to 1.5–6.6 mU. in six patients at 30 or to 60 minutes after incision. Thus, the levels of plasma ACTH during the course of anesthesia and surgery did not increase gradually, but consisted of two or three rapid, transient peaks.

The authors of reports in the literature estimated plasma ACTH levels only once during the course of surgery; no determinations during anesthesia alone were made; therefore, they failed to detect the effects of anesthetics on plasma ACTH, and missed the transient

TABLE 2. Effects of Ether Anesthesia and Surgery on Levels of Free Cortisol in Plasma (microgram/100 ml. = μg./dl.) in Ten Patients

Cases	Time (minutes)										
	Pre. Ind.	Anes. 10	20	30	Op. 5	30	60	90	120	Op. End	30
1	8.0	15.0	22.5	20.5	—	23.0	25.5	27.8	—	26.4	—
2	13.0	13.0	15.0	—	16.0	14.0	12.0	15.0	24.0	26.0	—
3	12.0	12.0	14.0	—	14.0	15.0	10.0	13.0	15.0	20.0	30.0
4	17.4	—	17.4	19.2	17.4	29.5	26.2	30.2	32.0	33.0	30.5
5	8.0	—	15.2	12.0	14.0	16.8	20.0	21.0	23.2	—	24.0
6	15.6	13.1	20.0	—	—	21.8	17.5	21.8	25.0	—	45.6
7	18.7	7.5	7.5	25.0	—	15.6	21.8	25.0	—	—	25.0
8	19.1	17.9	13.0	17.0	—	17.1	30.7	25.6	25.6	32.1	30.0
9	16.4	11.6	27.1	—	26.0	28.6	40.7	40.0	—	—	40.7
10	16.4	14.2	15.0	19.1	17.9	—	29.3	25.6	25.0	—	24.3
Mean	14.5	13.0	17.2	18.8	17.6	20.2	23.4	24.5	24.3	27.5	31.3

and intermittent alteration in plasma ACTH activity.[7, 10, 11] For instance, Cooper and Nelson[7] found elevated plasma ACTH levels (0.9–4.7 mU., mean 2.0) half an hour after operation, which returned to normal by four hours. The mean plasma ACTH concentration was reported by Estep *et al.*[10] as 1.3 (0.4–5.5) mU. one hour after incision for laparotomy in 13 patients under several anesthetics: thiopental, cyclopropane, ether and halothane anesthesia; whereas Ney *et al.*[11] without describing anesthesia, observed an elevation of ACTH (0.42–1.16, mean 0.74 mU.) during surgical procedures in 11 patients.

Our findings of a transient rise in plasma ACTH levels during ether anesthesia coincide with those of others in the rat.[8] In addition, in experiments in the dog under stressful circumstances, ACTH secretion has been reported to rise intermittently.[9] ACTH given intravenously to man has a short biological half-life of 4–18 minutes,[21, 22] and causes an abrupt increase in steroid content in the adrenal vein within two or three minutes. Peak concentration is seen between the seventh and tenth minute after ACTH injection, followed by a rapid decline.[21] These data partly explain why ACTH levels changed rapidly during anesthesia and operation in our observations.

We observed that the peak of plasma ACTH concentration coincided with the highest plasma cortisol levels in six of ten patients. In the remaining four patients, peak ACTH levels preceded the peak concentration of free cortisol in plasma. As previously mentioned, the major discrepancy between the alterations in plasma ACTH and cortisol levels during anesthesia and surgery was that the former increased intermittently and the latter rose stepwise. In our study determinations of plasma ACTH activity were made at least every ten minutes during induction of anesthesia, and every 30 minutes during operation; therefore, our data do not necessarily reflect the exact times of elevation of plasma ACTH levels. It is possible that the increase of plasma ACTH might have begun prior to blood sampling.

Liddle *et al.*[23] reported that when the plasma ACTH level was maintained at 0.2 mU. by intravenous infusion, the plasma cortisol concentration ranged from 22 to 27 μg./100 ml. When the plasma ACTH level was maintained at 1.0 mU., cortisol levels increased to 35–45 μg./100 ml. These plasma ACTH levels were below our detectable ACTH concentrations. Ney *et al.*[11] speculated that a diurnal increase in cortisol secretion (14–27 μg./100 ml.) occurring in man during the early morning hours is attributable to ACTH concentrations of the order of 0.25 mU. It is conceivable, therefore, that even non-detectable levels of ACTH in plasma could stimulate the adrenal cortex to secrete cortisol. These observations explain the high cortisol level in

plasma at the time of non-detectable ACTH concentrations in our study.

There is general agreement that free cortisol in plasma increases during anesthesia, and further elevation of cortisol at the beginning of operation is followed by gradual increase. We also noted a tendency toward higher plasma ACTH activity during operation than during ether anesthesia alone. It is well documented that there are differences in individual response to anesthesia and operation in terms of plasma cortisol as influenced by anesthetic agent, severity of surgery and postoperative complications.[4,5] The rate of rise and eventual magnitude are obviously dependent upon these variables. However, we could find no correlation between the excitement phase or vascular status and the elevation of plasma ACTH activity during ether anesthesia.

It is generally conceded that the plasma cortisol response to anesthesia and operation is due mainly to stimulation of the pituitary-adrenal system and increased secretion of cortisol.[5] Our data clearly indicate that the increase in plasma ACTH have a relationship to the rise in free cortisol in plasma.

Summary and Conclusions

Determination of plasma ACTH activity and concentrations of free cortisol in plasma were made simultaneously before induction of diethyl ether anesthesia, during and after induction of anesthesia, during laparotomy, and after the end of operation in ten patients. ACTH concentration before anesthesia was low at a non-detectable level below 1 mU./100 ml. ACTH levels during diethyl ether anesthesia increased remarkably but transiently, from 0.8 mU. to 2.0 mU. The elevation of plasma ACTH levels was of a bi- or triphasic nature, whereas the increase of plasma free cortisol was stepwise. It was apparent that the increased levels of free cortisol in plasma were due to the rise of plasma ACTH activity caused by stimulation of the anterior pituitary gland.

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Drugs

PHEOCHROMOCYTOMA Prior to the introduction of adrenergic blocking agents, surgical operations on patients with pheochromocytoma carried mortality rates of 25 to 50 per cent; the former rate if the presence of the tumor was known and prepared for, the latter if its presence was unsuspected. Wide swings of pressure, from severe hypertension during handling of the tumor to hypotension after its removal, along with arrhythmias, are the chief hazards. Alpha-adrenergic blockade initiated several days prior to surgery helps prevent the hypertensive crisis and allows expansion of the plasma volume. Beta-adrenergic blockers can be given just prior to and during surgery to control the catecholamine-induced arrhythmias and to counter the tachycardia which results from alpha blockade and high catecholamine levels. Combined alpha and beta blockade, however, presents other problems. Blood loss in a fully-dilated system that cannot compensate by vasoconstriction and is not associated with the warning sign of tachycardia can be disastrous. Contrariwise, overtransfusion can lead to failure with beta blockade. Careful arterial and venous pressure monitoring and accurate measurement of blood loss can help avert these problems. *(Ross, E. J.: Safer Surgery for Patients with Pheochromocytomas, Amer. Heart J. 74: 443 (Oct.) 1967.)*

PHEOCHROMOCYTOMA Pheochromocytoma may cause death by cerebral hemorrhage, pulmonary edema, left heart failure, ventricular fibrillation, or renal failure. To minimize these fatal complications, elevated blood pressure must be reduced. Neither barbiturates, reserpine, hydralazine, veratrum, alkaloids, saluretics, amyl nitrite, nor hexamethonium should be expected to reduce the effects of catecholamines. Ergot derivatives, dioxane compounds, alkylamines (dibenzyline), and imidazoline derivatives (phentolamine) are useful adrenergic blocking agents. Methyldopa interferes with storage and release of catecholamines and is used in treatment of incurable pheochromocytomas. Halothane is the anesthetic agent of choice; adrenal steroids should be available during bilateral adrenalectomy. Postoperatively, vasopressin should be used after a maximal blood volume has been established. *(Rosenberg, J. C., and Varco, R. L.: Physiologic and Pharmacologic Considerations in the Management of Pheochromocytomas, Surg. Clin. N. Amer. 47: 1453 (Dec.) 1967.)*