PREDICTION OF ADRENAL HYPOFUNCTION IN ANAESTHESIA

T. OYAMA, M.D. AND M. TAKIGUCHI, M.D.

IT HAS BEEN SUSPECTED THAT PATIENTS with adrenocortical insufficiency have been increasing in number because of increased therapeutic use of adrenal steroids and the performance of adrenalectomy or hypophysectomy for treatment of certain diseases. This has produced a growing probability of encountering iatrogenic diseases or disorders. Among them adrenal insufficiency during or after anaesthesia and surgery is the most dangerous complication, characterized mainly by arterial hypotension and tachycardia and terminating in shock or death.[1]

Therefore, if we could find an appropriate method of predicting adrenocortical hypofunction preoperatively, it would improve the safety of anaesthetic management of steroid-treated patients. The present study was undertaken to investigate a possibility to predict and to prevent adrenal hypofunction during anaesthesia in patients treated with steroid.

METHOD

Seventy-nine subjects were involved; 30 subjects served as controls, and 39 patients previously treated with steroid who underwent various operations were studied, as shown in Table I. These 39 patients had been treated with steroid at some period up to 8 years prior to operation. The total amount of glucocorticoids expressed as equivalent to cortisol ranged from 1.0 gm to 732.4 gm. None of them received steroids on the day before operation or on the day of surgery. In addition a group of ten patients who had no history of steroid therapy in the past and who had operations served as a control.

Each patient in both groups was premedicated with pentobarbital 50–100 mg orally at night and 1½ hours prior to the induction of anaesthesia. Meperidine 35 mg and atropine 0.5 mg were given by intramuscular injection 1¼ hours before the induction of anaesthesia. Due to the diurnal variations of the concentration of free cortisol in the plasma in man, induction of anaesthesia was started at 8:30 AM. Anaesthesia was induced with halothane (0.5–2 per cent), nitrous oxide (2 litres/min), and oxygen (2 litres/min) under a mask, followed by succinylcholine chloride (SCC) 40 mg intravenously for endotracheal intubation. Anaesthesia was maintained with halothane, nitrous oxide, and oxygen, combined with intermittent SCC injection whenever needed. Ventilation was controlled or assisted throughout the procedure. A moderate depth of anaesthesia was maintained during each procedure by clinical judgment and occasional electroencephalographic monitoring.

Determination of free cortisol (17-hydroxycorticosteroid = 17-OHCS) concentration in 1 ml plasma by Rudd's fluorimetric method[2] and six blood sampling times were similar to that previously reported.[1] For the protection of adrenocor-

*Department of Anaesthesia, Hirosaki University School of Medicine, Hirosaki, Aomori-Ken, Japan.

TABLE I

STEROID-TREATED PATIENTS

Cases	Age	Sex	Operation	total doses*	Duration (days)	Withdrawal† duration
1	24	F	V-A shunt	1,075	7	continue
2	57	M	Choledochostomy	1,350	23	17
3	22	M	Splenectomy	1,592	28	2
4	54	F	Hysterectomy	—	—	30
5	48	M	Gastrectomy	2,250	50	180
6	43	M	Choledochostomy	1,200	20	continue
7	57	M	Amputation of rectum	12,268	297	7
8	36	F	Hysterectomy	732,462	234	continue
9	17	M	Lymphadenectomy	5,000	86	12
10	45	M	Extirp. of parotid tumor	5,880	70	21
11	62	M	Choledochostomy	2,010	73	15
12	25	M	Pancolectomy	6,920	76	continue
13	22	F	Oophorectomy	4,847	83	8
14	27	M	Pancolectomy	7,040	168	continue
15	68	F	Extirp. of mediastinal tumor	—	—	—
16	54	M	Cholecystectomy	28,600	119	69
17	17	F	Splenectomy	24,000	557	continue
18	24	M	Bone plantation	45,704	ca 8yrs.	continue
19	26	M	Exploratory laparotomy	15,040	125	continue
20	21	M	Ileoproctomy	22,160	270	continue
21	38	M	Extirp. of retroperitoneal tumor	—	—	—
22	35	M	Exploratory laparotomy	4,020	44	continue
23	32	F	Hysterectomy	*ca.* 8,000	ca 50	2yrs.
24	19	F	Sympathoganglionectomy	1,060	37	30
25	31	F	Sigmoidectomy	6,960	146	75
26	36	M	Extirp. of laryngeal tumor	6,520	209	continue
27	40	F	External drainage from gallbladder	17,360	85	12
28	36	M	Bronchoscopy	8,240	241	continue
29	53	F	Exploratory laparotomy	5,360	90	continue
30	48	F	Pyelolithotomy	30,300	*ca.* 5yrs.	continue
31	25	M	Exploratory laparotomy	2,640	40	8
32	46	M	Craniotomy	6,840	52	continue
33	32	F	Laminectomy	6,060	77	continue
34	16	M	Anterolateral decompression	1,600	20	continue
35	16	M	Anterolateral decompression	2,400	25	continue
36	34	F	Hemithyroidectomy	6,160	206	182
37	36	M	V-A shunt	3,320	66	2
38	63	M	Ureterocutaneostomy	9,320	94	7
39	36	M	Cholecystectomy	2,960	51	16

*Equivalent doses to cortisol (mg).
†Days after the last steroid administration prior to one day before operation.

tical function, an ACTH test was performed in 44 subjects including 30 control subjects who were free from endocrine, hepatic or renal disease and who underwent neither surgery nor anaesthesia. The remaining 14 steroid-treated patients underwent operations. Synthetic ACTH [β^{1-24} ACTH, synacthen] was used. Immediately after withdrawing 3 ml of venous blood at 8:30 AM, ACTH 0.25 mg was injected intramuscularly and 3 ml of blood was withdrawn again 30 minutes after ACTH injection. The plasma cortisol concentration of these samples were determined as an index of adrenocortical function.

RESULTS

ACTH-test. The mean control cortisol level in the plasma at 8:30 AM was 14.9 ± 0.5 μg per 100 ml (±SE) in the 30 untreated control subjects. It increased sig-

nificantly to 20.4 ± 0.7 μg per 100 ml at 30 minutes after intramuscular injection of 0.25 mg of ACTH ($p < 0.001$) as shown in Figure 1. In the 14 steroid treated patients, the corresponding mean values of plasma cortisol were 12.6 ± 1.7 μg, and 14.7 ± 2.1 μg ($p < 0.05$) per 100 ml respectively, elevation in plasma corti-

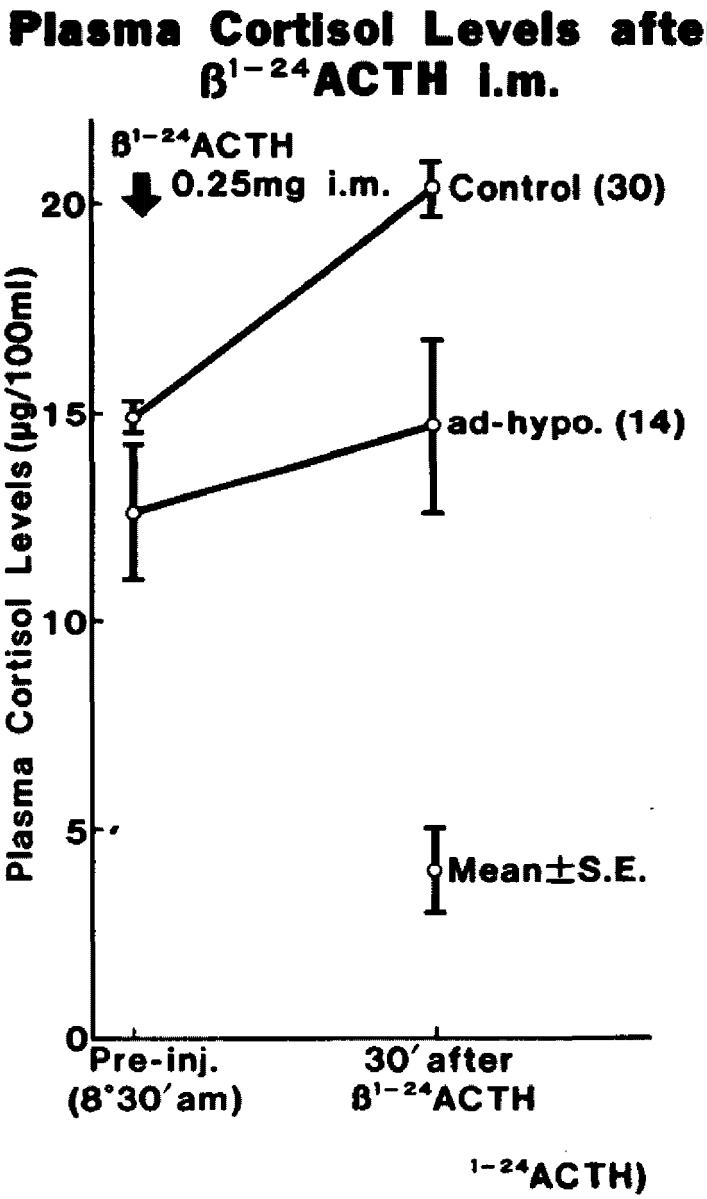

FIGURE 1

sol level ($p < 0.001$) after ACTH stimulation being less marked than in the subjects who had not been treated with steroid.

Preanaesthetic plasma cortisol level. In the steroid treated group the mean preanaesthetic level of free cortisol at 8:30 AM on the day of operation was 11.6 μg and was slightly higher than the control group (10.8 μg), but the difference was not statistically significant (Table II).

Plasma cortisol levels during anaesthesia. In the 39 patients to whom steroids had been given, the mean concentration after 30 minutes of halothane anaesthesia actually did not change from preinduction values (Table II). In the control non-steroid patients, the corresponding mean value increased significantly to 17.5 $\pm$ 1.6 μg from the mean preinduction value of 10.8 $\pm$ 1.4 μg per 100 ml ($p < 0.01$). In the steroid treated patients average free cortisol levels in the plasma further decreased to 10.0 $\pm$ 1.4 μg after 45 minutes of halothane anaesthesia. Moreover, the mean level of the control group was almost 1.4 times as high as that of the steroid treated group ($p < 0.05$) as shown in Table II.

Plasma cortisol levels during surgery. In the 39 steroid treated patients, the mean cortisol levels in the plasma at one hour after starting surgery was 16.0 $\pm$ 1.3 μg per 100 ml. It was 26.3 $\pm$ 1.8 μg per 100 ml in the ten control patients ($p < 0.01$) (Table II, Figure 2).

Discussion

Adrenocortical insufficiency during or after surgery has rarely been documented. Many hypotensive patients have had satisfactory responses to the administration of corticoids along with other measures and this has been interpreted as establishing the diagnosis of adrenocortical failure, with no proof other than the response to therapy.[8–11] Confirmation that such episodes are attributable to adrenal failure can come only from a study of plasma cortisol levels during shock or hypotension. Direct evidence of this has been scanty and difficult to acquire.[1,12–19] In many of these cases, which superficially resemble adrenal insufficiency, the patients recover after the correction of blood loss or injection of vasopressor.[20] Cope[15] called this sort of case a pseudohypo-adrenalism. There are several points to be resolved: (a) The frequency of arterial hypotension during or after operative stress in patients previously treated with steroid, when no steroid is given. (b) Relationship between the operative hypotension and adrenal insufficiency. (c) Factors which contribute to adrenal failure under surgical stress, including the duration of steroid treatment, the dosage and the method of administration. (d) Practical and reliable method to predict adrenal insufficiency.

Mattingly and Tyler[16] collected 14 operative and 23 medical emergency cases of patients who has previously had steroids and who collapsed. Their plasma cortisol levels were within normal limits (20 μg) and were recovered by injections of cortisol. Therefore, the usually operative hypotension in these patients does not seem to be the result of adrenal insufficiency, and the postoperative collapse is very rarely associated with a low plasma cortisol. For these reasons it is of paramount importance to measure adrenocortical function during hypotensive episodes in patients who have a past or present history of receiving steroid therapy.

TABLE II

COMPARISON OF MEAN FREE PLASMA CORTISOL LEVELS OF CONTROL WITH STEROID-TREATED PATIENTS DURING HALOTHANE ANAESTHESIA AND SURGERY

	Pre-ind.	Ane 15′	Ane 30′	Ane 45′	Ope. 30′	Ope. 60′	Ope. 120′	R.R.†
	Mean ± S.E.							
Control (10)	10.8 ± 1.4*	—	17.5 ± 1.6	—	—	26.3 ± 1.8	31.7 ± 2.2	32.7 ± 2.2
Steroid-T (39)	11.6 ± 1.0*	11.8 ± 1.6	12.5 ± 1.0	10.0 ± 1.4	15.0 ± 1.1	16.0 ± 1.3	21.1 ± 1.9	18.6 ± 1.5
t	0.392	—	2.350	—	—	3.705	3.339	5.200
p	N.S.		<0.05			<0.001	<0.01	<0.001

S.E.*: standard error of the mean.
†: patients were adequately awake in the recovery room.
N.S.: statistically not significant.

Plasma Cortisol Levels of Steroid-Treated Patients during Halothane Anesthesia & Surgery

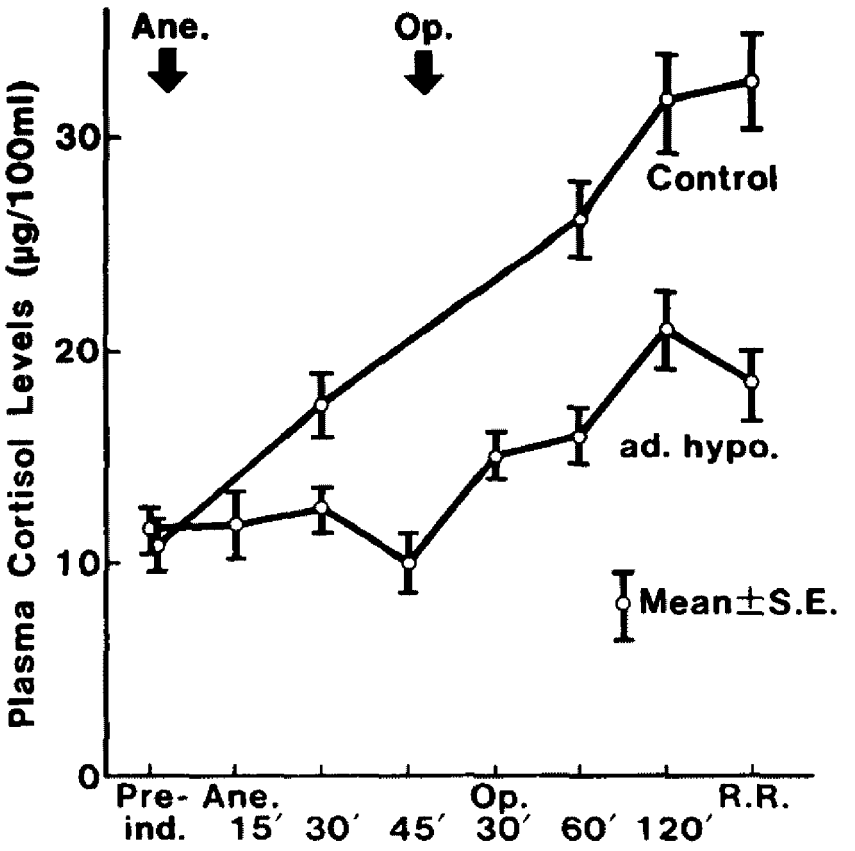

FIGURE 2

According to our criteria of normal adrenocortical function by rapid ACTH test (Table III), seven out of thirteen patients were judged as having hypofunction, and hypotension was observed in three patients. Arterial hypotension occurred in twelve patients (systolic blood pressure less than 90 mm Hg) during anaesthesia or surgery in 39 steroid treated patients. In nine cases out of twelve these hypotensive patients showed low plasma free cortisol levels (less than 15.5 µg per 100 ml) during the procedure. However, so far as the timing of hypotension is concerned, it is not necessary that the lowest plasma cortisol level correspond in time

TABLE III

CRITERIA OF NORMAL ADRENOCORTICAL FUNCTION BY ACTH RAPID TEST

(1) Control Plasma 17-OHCS	>12.0 μg/100ml
(2) Plasma 17-OHCS 30' after ACTH (0.25 mg im)	>17.0 μg/100ml
(3) (2)–(1)	> 5.0 μg/100ml
More than 2 Conditions	

with the arterial hypotension. None of them went into shock, and their condition was improved without using any corticosteroid except in one case.

As mentioned before, our data would suggest that low plasma free cortisol levels in the peripheral venous blood during anaesthesia or surgery are not necessary to represent arterial hypotension, and vice versa in the steroid treated patients.

Sampson *et al.*[13,14] could not find any significant difference in plasma cortisol levels during operation under thiopentone nitrous oxide anaesthesia between 18 steroid treated patients (from 10 days to 2 years for ulceritive colitis) and 17 untreated patients. They could not detect any significant difference in pituitary-adrenocortical function by a 6-hour ACTH test preoperatively. However two out of three patients who had demonstrated inadequate response to the ACTH test and had not received steroid cover preoperatively, suffered collapse immediately after the start of surgery and were relieved by intravenous injection of hydrocortisone.

Jasani *et al.*[17] applied a rapid synthetic ACTH test and other evaluating methods to 21 patients treated with steroid for rheumatoid arthritis, and 21 untreated patients. All of them underwent anterior synovectomy under thiopentone-halothane-N_2O anaesthesia. They found that the patients whose ACTH test was subnormal demonstrated least increase in plasma cortisol level, but it was not necessarily connected with hypotension. They emphasized pre-operative steroid cover for the patients who demonstrated subnormal response to ACTH test.

Plumpton *et al.*[19] failed to find significant differences in adrenocortical function by insulin test between steroid treated patients and untreated patients. They suggested that collapse will not occur 2 months after stopping steroid, and they advocate steroid cover for patients whose steroid withdrawal period is within 2 months prior to operation, except for patients who show normal response to the insulin hypoglycemia test.

It has been widely recommended that patients receiving steroids within two years of operation should receive steroid cover to prevent adrenal failure.[8] Vandam and Moore[20] stated that any patient who has been on cortisone therapy for four days or longer or cortisone therapy within the past six months may be considered to have subnormal adrenocortical function. Danowski *et al.*[21] observed that as much as 300 mg of cortisol daily for 30 days had no detectable effect on the ACTH response. According to them, after courses lasting a year or more spontaneous revival of adrenocortical activity will usually occur within 48 hours. There seems to be fairly general agreement that the pituitary-adrenal axis is little disturbed after short courses of steroid therapy.

However, we must not use conclusions on adrenal recovery to predict an adequate reaction to stress. The response to severe stress calls for greater corticotrophin release than does the restoration or maintenance of normal adrenal activity. Subjected to severe stress, a normally responsive adrenal should raise the cortisol to above 30 μg/100 ml and in extreme cases to above 100 μg. It is said that operative stress needs as much as two to seven times the resting level of plasma cortisol.[15] Therefore, the pituitary-adrenal axis, when damaged by long-continued steroid therapy, will be inadequate for the demands of stress even though normal activity may be well within its scope. It has seemed reasonable to cover all such patients, thus providing steroids unnecessarily for many to safeguard the few.[8,20] However, the increased incidence of infection is to be seriously considered.

Analysing our data, we find that the duration of administration and doses of corticosteroids were variable; therefore it is quite difficult to draw a definite conclusion from our data. It appears reasonable to say that real adrenocortical failure is rare, and the hypotensive episodes during anaesthesia or surgery are not necessarily to be attributed to adrenocortical insufficiency.

From a review of our data and 40 other adrenal crises during or after operation reported in the literature, the following points emerge; (a) In 32 per cent of the total cases reported the patient had been treated with steroid for less than one month, and in 62 per cent for less than six months. (b) The total dose of steroid used (equivalent to cortisol) was less than 1 gm in only one patient. This indicates that it is rare to find so-called adrenal failure in the patient whose total steroid prior to operation was less than 1 gm. (c) Only five patients had received daily doses of steroid equivalent to less than 25 mg of cortisol: this suggests that patients whose daily dose of cortisol was less than 25 mg have fewer episodes of arterial hypotension than those whose daily dose of cortisol was more than 25 mg. (d) Most of the reported cases (70 per cent) occurred in the early period between 1952 and 1958 when intermittent or small dose maintenance regimens were not established. (e) Twenty-six patients (60 per cent) had been treated with steroid either continuously or within one week prior to operation, but none of them received steroid on the day of operation.[1]

Prediction of adrenocortical hypofunction There are many methods to detect pituitary-adrenocortical hypofunction including various ACTH tests, metyrapone (SU-4885) test, and insulin test. However, they are time-consuming procedures. Synthesized ACTH (Synacthen), with an amino acid chain length of 24, is free from the anaphylactic reactions. Besides, it takes only 30 minutes to take the second blood specimen; therefore it is rapid and convenient for both patient and physician.

The normal range by our ACTH test is as follows: (1) Plasma cortisol level is above 12.0 μg per 100 ml at 8:30 AM (2) Plasma cortisol level at 30 minutes after intramuscular injection of ACTH is above 17.0 μg per 100 ml. (3) The increase in plasma cortisol level after ACTH injection in comparison with pre-injection control level is more than 5.0 μg per 100 ml. If at least two of the above three conditions are fulfilled, that case is considered normal. The normal range of ACTH by Wood *et al.*[22] and Greig *et al.*[23] are a little higher than ours.

According to Amatruda *et al.*[24] decreased plasma and urinary cortisol levels in

the patients who have had prolonged steroid treatment are not always accompanied by decreased adrenocortical sensitivity to ACTH or depressed pituitary reserve to Metopirone. There are some cases of normal adrenocortical response to ACTH despite the decreased resting level in plasma cortisol or fall in sensitivity to metopirone.[14,24] On the other hand, there is a possibility that pituitary activity is normal in the hypo-adrenocortical patients.[25] It is commonly believed that the recovery in plasma ACTH is seen earlier than that in plasma cortisol level.[26]

Danowski *et al.*,[21] applying the Metopirone test in 196 steroid treated patients, could not detect any pituitary-adrenal hypofunction when cortisol 20 mg per day had been administered for several years. These patients underwent major surgical operation safely without receiving steroid cover. Amatruda *et al.*,[24] who had given prednisone 30 mg per day and ACTH-Z 40 units once every 2 days for 3 months, observed withdrawal syndrome at the time of termination of treatment. However, responses to ACTH and Metopirone test were normal, which suggests the difficulty in predicting adrenocortical function by the metopirone test.

Analysing these data, the present authors propose a method of preoperative steroid administration as shown in Table IV to prevent adrenal failure in patients who have had steroid treatment and are undergoing operation.

TABLE IV

PREOPERATIVE STEROID COVER

1. Subnormal to ACTH Test
2. Under Treatment (>1W)
3. Steroid >1M or >1GM in 6M
4. Addisonian
5. Adrex or Hypx or History

SUMMARY AND CONCLUSION

The present study was undertaken to investigate a possibility of predicting adrenal hypofunction and its prevention. Preoperative rapid synthetic ACTH test for measuring adrenal function was done for 30 control subjects not treated with steroid and 14 steroid-treated patients. The correlation between arterial hypotension during anaesthesia or operation and adrenocortical hypofunction in 39 patients previously treated with steroid was also studied. None of these patients received steroids on the day before operation or on the day of surgery. A group of ten patients who had no history of receiving steroid therapy and who underwent operations served as a control. Both groups of patients received the same premedication and halothane-N_2O anaesthesia.

The mean free cortisol level in the plasma after 30 minutes of halothane-N_2O anaesthesia alone (12.5 ± 1.0 μg per 100 ml) in the steroid treated patients slightly but significantly increased from the preinduction value (11.6 ± 1.0 μg per 100 ml), while in the control group it increased markedly from 10.8 ± 1.4 to 17.5 ± 1.4 μg per 100 ml. Plasma levels of cortisol one hour after the start of operation were significantly elevated (16.0 ± 1.3 μg) in the steroid treated patients, but in the control patients they rose more markedly to 26.3 ± 1.8 μg.

Arterial hypotension (systolic blood pressure less than 90 mm Hg) occurred in

twelve steroid treated patients during anaesthesia alone or during operation. However, it was not necessary that the timing of hypotension corresponded with the lowest plasma cortisol level. None of the hypotensive patients developed shock, and they recovered without steroid administration except in one case. These data would suggest that low plasma free cortisol levels in the peripheral venous blood during anaesthesia or surgery are not necessary to development of arterial hypotension in the steroid treated patients and vice versa.

According to our criteria by ACTH test, seven out of fourteen steroid-treated patients were judged as hypofunctional and hypotension was observed in three patients. In order to prevent a possible so-called adrenocortical insufficiency during operation in patients previously treated with steroid, the author suggests that the following patients should receive hormone preoperatively and during operation; (a) patients who showed subnormal response to ACTH test (b) patients currently under steroid treatment for more than one week (c) patients who have had continuous treatment for more than one month in the six months prior to operation or who have received more than 1 gm of cortisol or equivalent other steroids.

Résumé

La présente étude a été entreprise dans le but d'investiguer la possibilité de prédire l'insuffisance surrénalienne et d'instituer un traitement préventif. Au cours de la période pré-opératoire un test à l'ATCH synthétique fut fait chez 30 patients ne recevant pas de corticoïdes et servant de contrôle et chez 14 patients traités avec stéroïdes dans le but d'évaluer la fonction surrénalienne. La correlate entre l'hypotension survenant au cours de l'anesthésie ou de l'opération et l'insuffisance surrénalienne fut également étudiée chez 39 patients traités antérieurement avec des stéroïdes. Aucun de ces patients ne reçut de stéroïdes le jour précédent l'intervention ou le jour même de la chirurgie. Un groupe de 10 patients n'ayant aucune histoire de traitement aux corticoïdes et qui avaient à subir une intervention chirurgicale servirent de contrôle; les deux groupes de patients furent prémédiqués de la même façon et furent anesthésiés à l'halothane-N_2O.

Le taux de cortisol libre moyen dans le plasma après 30 minutes d'anesthésie à l'halothane-N_2O seulement (12.5 ± 1.0 μg par 100 ml) chez les patients traités aux corticoïdes augmenta légèrement mais de façon significative en regard des valeurs pré-anesthésiques (11.6 ± 1.0 μg par 100 cc), tandis que dans le groupe de contrôle, il augmenta de façon importante de 10.8 ± 1.4 à 17.5 ± 1.4 μg pour 100 cc. Les taux de cortisol plasmatique une heure après le début de la chirurgie étaient élevés de façon significative (16.0 ± 1.3 μg) chez les patients traités aux corticoïdes, tandis que chez les patients servant de contrôle ils augmentaient de façon plus importante, soit 26.3 ± 1.6 μg.

L'hypotension (pression systolique inférieure à 90 mmHg) survient chez 13 patients traités aux corticoïdes au cours de l'anesthésie ou durant l'opération. Cependant l'hypotension ne survient pas nécessairement alors que le taux de cortisol plasmatique était à son plus bas niveau. Aucun des patients ayant présenté de l'hypotension n'entra en choc et cet état se corrigea sans administration de corticoïdes sauf dans un cas. Ces données suggèrent qu'un taux de cortisol libre plas-

matique abaissé dans le sang veineux périphérique au cours d'une anesthésie ou de la chirurgie n'est pas nécessaire pour le développement d'une hypotension artérielle chez les patients traités aux stéroïdes et vice-versa.

Selon nos critères basés sur le taux à l'ATCH, sept sur treize patients traités aux stéroïdes furent considérés comme hypofonctionnels et on observa de l'hypotension chez 3 de ces patients. Dans le but de prévenir une insuffisance adrenocorticale possible au cours d'une opération chez les patients préalablement traités aux corticoïdes, l'auteur suggère que les groupes de patients suivants devraient recevoir un traitement normal suppléant en période pré-opératoire et au cours de l'opération: a) les patients qui présentent une réponse subnormale au test à l'ATCH, b) les patients en traitement aux corticoides depuis plus d'une semaine, c) les patients qui ont eu un traitement continu pour plus d'un mois au cours des six derniers mois précédant l'intervention ou qui ont reçu plus d'un gramme de cortisol ou l'équivalent d'un autre stéroïde.

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