Effects of Ketamine on Adrenocortical Function in Man

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KETAMINE (CI-581) is a new short-acting nonbarbiturate anesthetic agent, a derivative of phencyclidine. Reports on the effects of ketamine on cardiovascular or respiratory function have been published,[1-3] but no report on its effect on endocrine activity has appeared.

We have previously reported the effects of intravenous anesthetic agents, such as gamma-hydroxybutyrate,[4] propanidid,[5] and thiopental[4] on the adrenocortical function in man. The present study evaluates the effect of ketamine on adrenocortical activity judged by the plasma concentration of cortisol (17-OHCS), relating such findings to the effects of anesthesia and surgery.

METHODS

Twenty-one patients, ranging in age from 16 to 66 years, who were free from hepatic, renal, or endocrine disease, were studied. The patients were given 1 mg./kg. of oral pentobarbital at 7:00 a.m., 2 mg./kg. of meperidine and 0.5 mg. of atropine intramuscularly at 7:30 a.m., and anesthesia was induced at 8:30 a.m., after the first control blood sampling, by 2 mg./kg. of intravenous ketamine injected for 1 minute. After injection of 60 to 120 mg. of ketamine, approximately 2 minutes after starting anesthesia, 40 mg. of succinylcholine chloride were injected to facilitate endotracheal intubation. For the maintenance of anesthesia, intermittent intravenous administration of 1 mg./kg. of ketamine was supplemented by nitrous oxide (3.5 L./min.) and oxygen (1.5 L./min.) An average total of 497 mg. of ketamine (range 225 to 900 mg.) was employed. Respiration was assisted or controlled throughout the procedure, and 21 to 30 mg. of curare were used as required for muscle relaxation for abdominal cases.

Table 1 shows the surgical procedures included in the study, average duration of anesthesia, and total ketamine used. Low molecular weight dextran (500 ml.) was

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TABLE 1
Patients and Procedures (Ketamine)

Number	Age	Sex	Operation	Operation time	Anesthesia time	Total doses, mg.
1	18	F	Osteotomy	2:40	4:20	900
2	29	F	Lymphadenectomy	4:24	5:49	550
3	41	F	Oophorectomy	1:11	2:45	280
4	18	F	Arthrodesis	0:33	1:45	400
5	66	M	Thyroidectomy	3:35	4:55	675
6	44	F	Mastectomy	1:05	5:04	550
7	66	F	Panhysterectomy	3:05	5:20	920
8	29	F	Mastectomy	1:34	3:19	390
9	61	F	Hysterectomy	2:10	3:00	450
10	51	F	Gastrectomy	1:35	2:55	300
11	42	F	Panhysterectomy	2:55	4:00	380
12	49	F	Hysterectomy	2:05	3:35	225
13	26	F	Hemangioma removal	2:05	3:07	240
14	35	M	Spinal fusion	—	1:10	300
15	42	F	Hysterectomy	2:18	3:37	550
16	47	F	Hysterectomy	2:45	4:00	450
17	24	F	Ligamentum resection	1:40	2:50	310
18	31	F	Panhysterectomy	3:20	3:55	500
19	34	M	Gastrectomy	3:35	5:00	720
20	16	M	Decompression	1:15	2:00	600
21	57	M	Gastrectomy	4:00	5:20	750
Mean				2:23	3:42	497

infused during the procedure. Blood was transfused to replace blood loss of over 500 ml. No appreciable cardiovascular depression was noted, judged by the arterial blood pressure and electrocardiogram during anesthesia. In addition, we could find no evidence of either anoxia or hypercarbia in the arterial blood-gas samples.

Blood was sampled at 8:30 a.m., just before induction; 10 minutes and 30 minutes after anesthesia alone; 30 minutes, 1 hour, and 2 hours after the start of operation; and when the patient had adequately awakened in the recovery room. Venous blood (1 ml.) was obtained in a heparinized syringe and centrifuged within 30 minutes. The free cortisol (17-hydroxycorticosteroid) = 17-OHCS = hydrocortisone) in 0.05 ml. of plasma was determined according to the method of competitive protein binding radioassay of Murphy,[6] with a Beckman liquid scintillation counter. The duplicate error in our method was ± 1.5 mcg./100 ml. of plasma, which appeared reliable for the analysis of our data.

RESULTS

The free-cortisol levels at 8:30 a.m., just before induction, averaged 15.8 ± 1.1 mcg./

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TABLE 2
Plasma Cortisol Levels in Ketamine-Nitrous Oxide-Oxygen Anesthesia and Surgery

Case	Preinduction	Time after start of anesthesia		Operation, mcg./100 ml.			Recovery room
		10 minutes	30 minutes	30 minutes	60 minutes	120 minutes	
1	25.0	17.5	16.5	36.0	29.5	30.0	30.0
2	13.0	18.0	30.0	24.0	24.5	24.0	—
3	12.0	—	21.5	—	24.0	—	29.5
4	14.0	—	—	38.0	—	—	31.5
5	15.5	18.0	—	20.0	29.0	—	25.0
6	20.0	20.0	22.5	22.5	35.0	—	25.0
7	5.0	17.5	—	21.0	—	26.5	—
8	16.5	—	22.5	—	—	—	—
9	19.5	—	21.0	33.0	34.5	—	—
10	16.0	—	19.0	25.0	24.0	—	23.5
11	15.5	—	24.0	32.0	30.0	17.5	25.0
12	13.1	—	25.0	30.0	26.0	28.0	—
13	10.0	—	17.5	15.0	30.0	—	29.5
14	9.5	—	25.5	—	—	—	28.0
15	23.0	27.0	27.5	32.5	36.5	33.5	36.0
16	19.0	—	18.0	20.0	18.5	22.5	20.0
17	17.0	18.0	18.0	16.0	18.0	—	20.5
18	21.5	17.0	26.5	26.5	25.5	25.0	19.0
19	9.0	9.0	5.0	10.0	21.0	25.5	24.0
20	18.0	17.0	16.0	25.5	20.0	—	35.0
21	19.0	25.5	15.0	35.5	25.3	36.5	41.0
Mean	15.8	18.6	20.6	25.7	26.5	26.9	27.7
S.E.	1.1	1.4	1.3	1.8	1.3	1.6	1.5
P*		Not significant	0.02	0.01	0.01	0.01	0.01

*Compared with preinduction value.

100 ml. of plasma (± = standard error of the mean) (table 2). The level increased slightly (2.8 mcg.) at 10 minutes after anesthesia alone and elevated significantly to 20.6 ± 1.3 mcg. ($p < 0.02$) 30 minutes after the start of anesthesia but before operation. It increased gradually and significantly ($p < 0.01$) to 25.7 ± 1.8 mcg., 26.5 ± 1.3 mcg., and 26.9 ± 1.6 mcg.; 30 minutes, 1 hour, and 2 hours, respectively, after the start of the operation. It further rose to 27.7 ± 1.5 mcg. ($p < 0.01$) in the recovery room when the patients were considered to have fully awakened (figure).

DISCUSSION

An increase in plasma cortisol level has been shown during operation under general anesthetic technics.[7] The new intravenous anesthetic adjuvant, gamma-hydroxybutyrate, causes a preoperative rise.[4] On the other hand, thiopental and the nonbarbiturate ultrashort-acting agent, propanidid, have the least stimulating effect on adrenocortical activity.[5]

The adrenocortical stimulation, as judged by the elevation of the cortisol level, resembles that of gamma-hydroxybutyrate.[4] Both these agents tend to increase arterial blood pressure during anesthesia.[4] Domino and associates[1] and Corssen and Domino[2] found transient elevations in arterial blood pressure in surgical patients, suspecting the

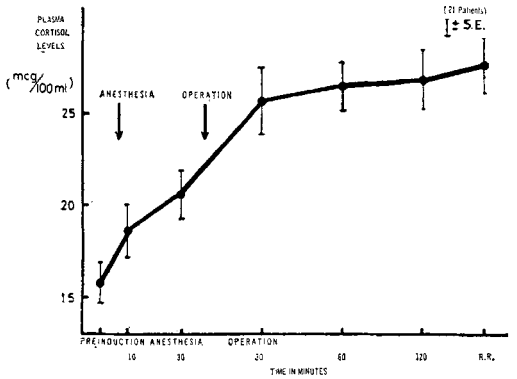

FIG. Effects of ketamine-nitrous oxide anesthesia and surgery on plasma free cortisol levels in man.

possibility of sympathetic stimulation by ketamine. We would suggest that the adrenocortical stimulation by ketamine might account for the increased arterial blood pressure.

It is known that cortisol is essential for maintaining the normal cardiovascular response to stress.[8] Thomas and Brockman[9] and Spink and Vick[10] hypothesize a possible additive function of cortisol to catecholamine. Lillehei and coworkers[11] and Schumer and Sperling[12] demonstrated that cortisol increases cardiac output in animals and in man.

In contrast to thiopental, ketamine does not evoke bronchospasm, tends to elevate arterial blood pressure and raise the pain threshold, and is injectable intramuscularly. At the same time, this agent has some disadvantages, such as transient respiratory depression, which lasts for 1 to 2 minutes after injection and somnolence and prolonged sleep with dreaming during the postoperative period.

SUMMARY AND CONCLUSIONS

The present report evaluates the effect of ketamine combined with nitrous oxide-oxygen anesthesia on adrenocortical function, as judged by the influence on plasma free-cortisol levels in 21 patients undergoing operation. Ketamine-nitrous oxide-oxygen anesthesia alone for 30 minutes significantly stimulated adrenocortical activity; adrenocortical stimulation was further accentuated during surgical intervention and after operation. A possible relationship between the tendency of arterial hypertension caused by ketamine and adrenocortical activity is also discussed.

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The first point of wisdom is to discern that which is false; the second to know that which is true.

—*Lactantius*