PITUITARY BLOCKADE BY MEPERIDINE IN MAN

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BRIGGS and Munson [1] have reported that, in rats, the depressant effects of morphine on the hypothalamus cause a diminution of secretion of ACTH by the pituitary that results in depressed adrenocortical function.

A more recent report by McDonald and coworkers [2] has also shown that the pituitary effect of therapeutic doses of morphine on ACTH release in man is a suppressant one and results in lowering significantly the plasma 17-OH corticosteroid levels.

Although meperidine has been widely used as a preoperative medicant and a postoperative analgesic agent, no data have been published regarding its effect on adrenocortical function. Meperidine-supplemented nitrous oxide anesthesia is frequently used and is a useful technique in certain types of geriatric surgery.

We undertook, therefore, to investigate the effect of meperidine and meperidine-supplemented nitrous oxide anesthesia on adrenocortical function in patients undergoing surgery. Adrenocortical function was assayed by measuring free plasma 17-OH corticosteroid levels and by tests of the adrenal cortical capacity. The effect of anesthesia and operation on the rate of disappearance of intravenously administered hydrocortisone was also determined.

METHODS

In unpremedicated patients about to undergo elective operation, venous blood samples were obtained before the induction of anesthesia. The subjects were then given 50 to 200 mg. of meperidine intravenously in several intermittent doses and, with topical anesthesia, were intubated by either the orotracheal or the nasotracheal route, depending upon the surgical need. Nitrous oxide was administered in a 70 to 75 per cent delivered concentration with oxygen in a semiclosed circle carbon-dioxide absorption system. Meperidine was injected intravenously in intermittent doses to a total of 25 to 100 mg. hourly depending upon the subject's tolerance to meperidine. Hypoxia and carbon dioxide retention occurred in two cases due to the airway obstruction; otherwise, all subjects were maintained in a state of adequate ventilation throughout as determined by clinical observation. Another venous sample was drawn 15 to 30 minutes following the induction of anesthesia alone, and others during operation at regular intervals.

Adrenal cortical response was tested in another group of patients by the intravenous infusion of a maximally stimulating dose of ACTH over half an hour period preoperatively and again during anesthesia and the surgical procedure. The ACTH employed was "Corticotropin Injection" (ACTH) (Upjohn), in a concentration of 25 I. U. in 200 ml. of 5 per cent dextrose in water. Venous blood samples were drawn for determination of plasma 17-OH corticosteroid levels before, and at two, four, and six hours after the infusion was started.

The rate of disappearance of intravenously administered hydrocortisone was studied in several other patients one or two days before operation. After the injection of 100 mg. of Solu-Cortef (Upjohn), venous samples were drawn at 15 minutes, one, three, five, and seven hours to follow the plasma 17-OH corticosteroid levels. Later, during meperidine-nitrous oxide anesthesia and operation, the same patient received the same test dose of hydrocortisone.

Plasma 17-OH corticosteroid levels were determined by the method of Silber and Porter, as modified by Peterson *et al.*[3]

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TABLE 1

CHANGES IN FREE 17-OH CORTICOSTEROIDS IN PLASMA DURING MERPERIDINE-N_2O ANESTHESIA AND SURGERY

Patient	Control	Anesthesia Only			Operation			Postoperative	
	17-OH (μg./100 ml.)	Time (hours)	Mep. (mg.)	17-OH (μg./100 ml.)	Time (hours)	Mep. (mg.)	17-OH (μg./100 ml.)	Time (hours)	17-OH (μg./100 ml.)
A	21.0	¾	150	17.8	3¾	450	8.6	—	—
B	41.0	3	350	21.0	½	0	30.0	2	38.0
C	19.0	3	300	30.0*	2	25	17.1	24	36.0
D	43.7	1¾	350	33.4	1	100	26.4	1	40.0
E	32.6	1¾	300	35.8	½	0	40.4	1	33.4
F	24.7	4½	500	17.6†	2	200	46.6	1	40.5

* Transient airway obstruction during induction.
† Prior to asphyxia while doing nasotracheal intubation (fig. 2).

RESULTS

In a series of 23 normal adults, early morning blood samples showed a normal distribution of plasma levels of 17-OH corticosteroids with the mean at 13 μg. per cent. Since the log-normal distribution produces an unsymmetric standard deviation on the two sides of the mean, the range of one standard deviation from the mean extended from 9 to 18 μg. per cent.

A series of 21 unselected patients unpremedicated on the morning of operation had a mean plasma 17-OH corticosteroid level of 23 μg. per cent with the one standard deviation range extending from 16 to 34 μg. per cent. In the patients who cooperated in this study, the preoperative control levels were still higher with a mean of 33 μg. per cent and a standard deviation range from 24 to 44 μg. per cent.

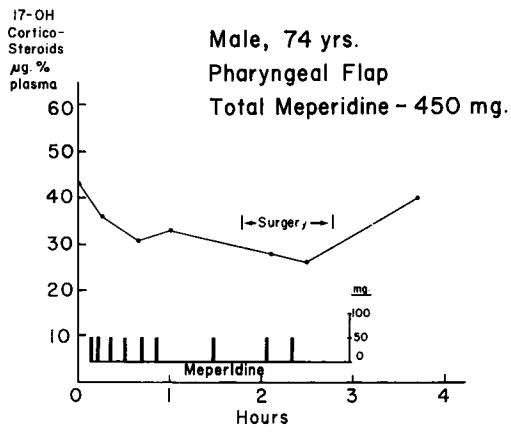

FIG. 1. Effects of anesthesia with meperidine-N_2O and of operation on the plasma 17-OH corticosteroid levels. Inset indicates dose schedule of meperidine.

In four out of six surgical patients anesthetized with meperidine-nitrous oxide prior to operation, the plasma levels of 17-OH corticosteroids decreased gradually when meperidine was continued in intermittent doses of 50 to 100 mg. per hour (table 1). However, in no case did the level decrease below the normal limits of the free plasma 17-OH corticosteroid levels. One patient (*E*) showed a small rise in free plasma 17-OH level during anesthesia and also during operation. With surgical intervention, three out of the six subjects showed small declines in the plasma 17-OH corticosteroid levels (fig. 1). One patient (*B*) whose level declined during anesthesia alone recovered part of this decline during operation.

In the sixth patient, (*F*) an episode of severe hypoxia and carbon dioxide retention resulting from obstruction of the airway produced a gradual but marked rise in 17-OH corticosteroid level (fig. 2). This progressive subsequent rise was not affected by immediate correction of the airway obstruction and administration of 100 per cent oxygen or by the subsequent administration of 100 to 150 mg. of meperidine in divided doses.

Four patients anesthetized with minimal intravenous doses of meperidine for induction and maintained at rates of 25 mg. of meperidine per hour during cyclopropane and curare supplemented nitrous oxide anesthesia showed

TABLE 2

CHANGES IN FREE 17-OH CORTICOSTEROIDS IN PLASMA DURING MEPERIDINE–CURARE–CYCLOPROPANE–N_2O ANESTHESIA AND SURGERY

Patient	Control	Anesthesia Only			Operation		
	17-OH (μg./100 ml.)	Time (hours)	Meperidine (mg.)	17-OH (μg./100 ml.)	Time (hours)	Merepidine (mg.)	17-OH (μg./100 ml.)
G	34.1	1	150	40.1	1½	50	46.8
H	35.7	1	150	34.1	3	75	40.7
I	19.5	1¾	150	23.0	½	25	24.3
J	21.5	½	125	19.3	1½	25	22.4

little change in the plasma 17-OH corticosteroid level either with or without surgical intervention (table 2). On the other hand, the plasma 17-OH corticosteroid levels rose gradually as the meperidine effect wore off during the immediate postoperative period.

Standard ACTH response tests on four surgical patients one or two days before operation produced a normal rise in plasma 17-OH corticosteroid levels (table 3). In each case, the same test during meperidine-nitrous oxide anesthesia and operation produced a greater rise in the plasma 17-OH corticosteroid levels than was obtained in the control test in the same patient.

Three surgical patients were given hydrocortisone as a test of the disappearance rate of hydrocortisone. On the average, the rate of disappearance was little different on the operative day than on the control day (fig. 3 and table 4).

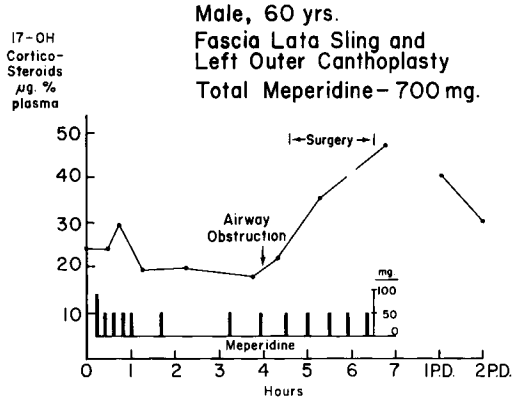

FIG. 2. Effect of brief airway obstruction on plasma 17-OH corticosteroid levels while anesthetized with meperidine-N_2O. Inset indicates dose schedule of meperidine. *1 P.D.* and *2 P.D.* are the levels on the first and second postoperative days.

DISCUSSION

The high control values for plasma 17-OH corticosteroids observed are believed to be a result of the nature of the operation contemplated. These particular patients were selected to provide studies of several hours duration and the procedures were radical resections of the head and neck. The loss of voice and features involved make the decision to undergo surgery very difficult and trying for the patient, and should elevate his adrenalin level over a considerable period prior to operation. However, these patients are capable of

TABLE 3

RESPONSE TO ACTH PREOPERATIVELY AND DURING OPERATION WITH MEPERIDINE–N_2O ANESTHESIA

Patient		Free 17-OH Corticosteroids (μg./100 ml. Plasma)			
		Control	After: 2 hours	4 hours	6 hours
K	Preop.	35.2	52.0	54.8	37.6
	Surg.	33.4	59.2	63.4	72.8
L	Preop.	35.4	62.3	69.6	42.6
	Surg.	39.6	57.2	79.0	88.0
M	Preop.	36.9	45.0	56.8	36.0
	Surg.	18.4	45.2	70.4	59.4
N	Preop.	32.4	40.4	40.4	34.6
	Surg.	32.4	58.4	56.4	50.0

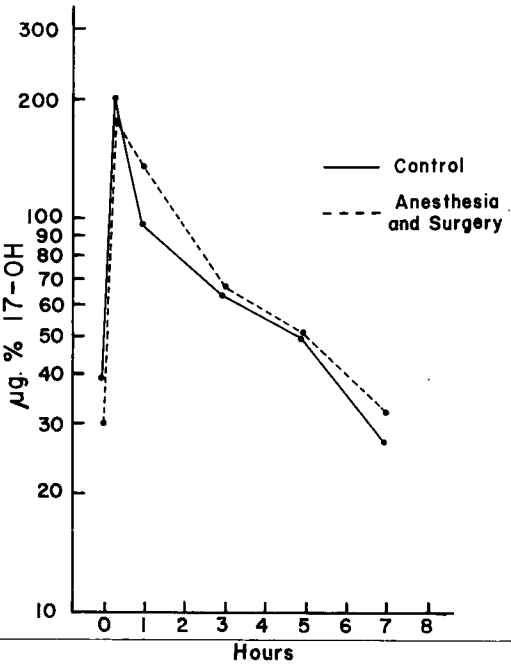

FIG. 3. Clearance rate of hydrocortisone from plasma after administration of a single 100 mg. dose intravenously. Control studies were done preoperatively.

reaching still higher levels under added stress or ACTH stimulation of the adrenals.

An increase in plasma 17-OH corticosteroids has been observed during the surgical procedure with every general anesthetic technique previously examined. Indeed, some general anesthetic agents cause a rise before operation is begun. On the other hand, when neural pathways from the surgical area are blocked by spinal or regional techniques or by hypothermia, a rise in 17-OH corticosteroids does not occur. These observations argue that the stress reaction is not abolished by general anesthesia although the patient is unconscious. Moreover, the response to operation depends upon intact neural pathways to the site of surgical injury and is not elicited by the central awareness of such injury provided by the special senses.[4] Meperidine appears to exert its blocking action on the stress reaction in the pituitary through the central nervous system rather than in the pituitary itself. Although adequate doses of opiates elevate the pain threshold and produce drowsiness, the stress response can still be elicited by asphyxia. Indeed, if the magnitude of the rise observed after transient asphyxia (fig. 2) is a criterion, the adrenal certainly and probably the pituitary as well, are not depressed at all.

Despite the slight decrease in plasma 17-OH corticosteroid levels observed during meperidine-nitrous oxide anesthesia, the adrenal cortex was stimulated by the surgical trauma. The administration of ACTH produced a greater rise in the levels of the plasma 17-OH corticosteroids during operation under meperidine-nitrous oxide anesthesia than that seen in the control data in the same patient. This elevated level also persisted a longer time than during the control test. However, the magnitude of rises were less than those observed by Sandberg and associates[5] during ACTH administration postoperatively. The greater rise during the postoperative period probably resulted from "priming" by the surgical stimuli.

The gradual increase in 17-OH corticosteroid level during operation and anesthesia has been attributed to disturbances in liver and kidney function.[6,7] Interference with the usual conjugation and excretion of the adrenal corticosteroids would increase their plasma concentration and especially the amount of the

TABLE 4

ELIMINATION OF INTRAVENOUS HYDROCORTISONE PREOPERATIVELY AND DURING OPERATION WITH MEPERIDINE–N_2O ANESTHESIA (FIG. 3)

Patient		Free 17-OH Corticosteroids (μg./100 ml. Plasma)					
		Control	15 min.	1 hr.	3 hr.	5 hr.	7 hr.
O	Preop.	48.1	—	88.6	68.4	48.2	41.7
	Surg.	39.1	—	132.8	—	64.8	18.2
P	Preop.	21.2	157.6	85.0	55.0	40.3	28.2
	Surg.	21.4	179.8	166.1	67.8	35.4	45.0
Q	Preop.	45.9	235.7	110.3	63.0	56.1	10.3
	Surg.	28.5	124.4	97.2	63.0	48.2	32.6
Average	Preop.	38.4	196.7	94.6	62.2	48.2	26.7
	Surg.	29.7	152.1	132.0	65.4	49.5	31.9

unconjugated form. These conjectures are seen to be unfounded unless one argues that meperidine improves liver and kidney function. The disappearance curves of intravenously injected hydrocortisone appear to indicate a dependence of the rate on concentration with a decay constant of 0.25 to 0.35 hour^{-1}. No essential difference in decay constants for the control day and the day of operation was found on re-examinating the data of Sandberg[8] which relate to the postoperative period. The decay constants of the control and postoperative periods are the same and in the range of 0.25–0.35 hour^{-1} (fig. 4). The base line concentration was higher in the postoperative period so more hydrocortisone was cleared per hour since the clearance rate is concentration dependent. This, however, does not mean the rate of clearance of endogenous hydrocortisone is increased.

Cyclopropane anesthesia has been shown to cause a gradual rise in the plasma 17-OH corticosteroid level by Moore.[9] However, cyclopropane-curare-nitrous oxide anesthesia together with intravenous doses of 25 mg. of meperidine per hour did not alter the plasma 17-OH corticosteroid level significantly either with or without surgical intervention. Thus meperidine in clinical dosage appears to suppress this hypophysial stimulatory effect of cyclopropane as well as that of the surgical stress.

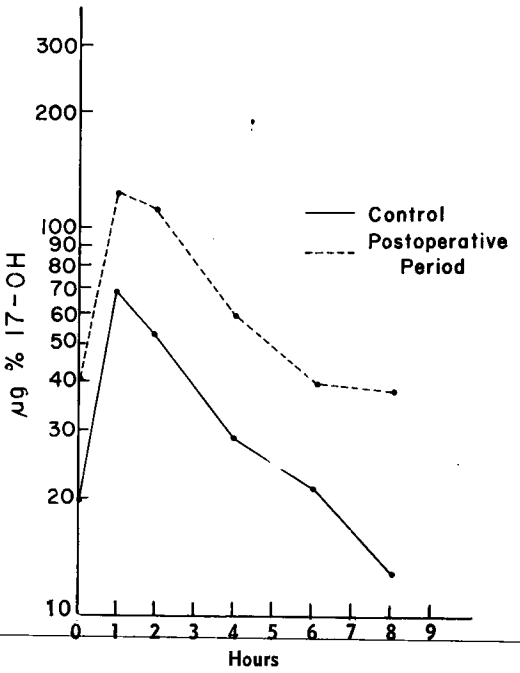

FIG. 4. Clearance rates of hydrocortisone in control and postoperative periods. Replotted from the data of Sandberg *et al.*[8]

SUMMARY

In patients about to undergo operation, the elevated 17-OH corticosteroid level observed was depressed after administration of meperidine intravenously at rates of 50 to 200 mg. per hour. In 5 out of 6 patients, little or no rise in 17-OH corticosteroid levels occurred after operation was started. The sixth patient showed an elevation of 100 per cent above the control level following transient asphyxia. Little change in the 17-OH corticosteroid level was observed during operation while meperidine was being administered intravenously at rates as low as 25 mg. per hour. ACTH test doses stimulated the adrenal to adequate response during meperidine administration. Hydrocortisone administered intravenously disappeared at identical rates in the same patient awake and during operation with meperidine anesthesia.

Thus, in man, meperidine in clinical dosage prevents the adrenal response to surgical stress. Like spinal and regional anesthesia, meperidine is believed to diminish the perception of peripheral noxious stimuli and so blocks their usual effect on the pituitary.

Merck, Sharp, & Dohme and Schering Corporation supplied steroids used in this study.

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CAROTID SINUS REFLEX In a group of 2,500 patients undergoing surgery of the neck, 24 per cent developed some manifestation of the carotid sinus reflex. The reflex occurred most often in hypertensive men over 50 years of age. Patients with myocardial or coronary disease showed the more radical drops in blood pressure and pulse. There was no relationship between the occurrence of the reflex and the administration of Rauwolfia, tranquilizers, preoperative medication, or anesthetic agents. Therapy for the reflex is: (1) Discontinuance of surgical stimulation. (2) Local injection of procaine to the carotid bulb. This blocks the afferent vagus, thus remedying the bradycardia, and also blocks the inhibition of the vasoconstrictor nerve, thus remedying the hypotension. (3) Intravenous injection of atropine. This produces partial inhibition of the efferent vagus, thus correcting bradycardia. Atropine also directly counteracts the hypotension of the reflex, presumably via its blocking effect on sympathetic cholinergic fibers. (4) Intravenous injection of vasoconstrictor drugs which, by their peripheral action, also counteract the hypotension. (*Selvin, B., and Howland, W. S.: New Concepts of Physiology of Carotid Sinus Reflex, J. A. M. A. 176: 12 (April 8) 1961.*)

CEREBRAL CIRCULATION In 17 patients with Cheyne-Stokes respirations, arterial oxygen saturation was lowest and carbon dioxide tension highest during the hyperpneic phase of respiration and, at this point, cerebral arteriovenous oxygen difference was decreased. The converse changes appeared in apnea. During hyperpnea, there was an increase in spinal fluid pressure and a reduction in circulation time across the brain. From encephalographic and clinical findings, it appears that the phasic alteration in cerebral circulation is the essential factor producing fluctuations in the patient's mental state, EEG and neurologic signs. (*Karp, H. R., and others: Cerebral Circulation and Function in Cheyne-Stokes Respiration, Amer. J. Med. 30: 861 (June) 1961.*)

ISOPROPYLARTERENOL The effect of isopropylarterenol hydrochloride (Isuprel) in the anesthetized dog on the left ventricular cardiac output and the total peripheral resistance is essentially the same whether the effect of Isuprel in producing a tachycardia is permitted or prevented. (*Nakaw, J., and others: Study of Mechanism of Increase in Cardiac Output Induced by Isopropylarterenol Hydrochloride (Isuprel), Proc. Soc. Exp. Biol. Med. 107: 172 (May) 1961.*)