EFFECT OF ETHRANE ANAESTHESIA AND SURGICAL OPERATION ON ADRENOCORTICAL FUNCTION

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THE PRESENT STUDY was undertaken to investigate the effect of Ethrane, a recently introduced halogenated ether, and of surgical operation on adrenocortical function by determining cortisol (= hydrocortisone) in the plasma of peripheral venous blood in man. Although other anaesthetic agents have been shown to have some influence on plasma free cortisol levels in man,¹⁻⁴ information on the effect of Ethrane anaesthesia has been scant. Only Dobkin *et al.*⁵ have reported a rise of mean plasma cortisol levels in patients undergoing Ethrane anaesthesia.

METHOD

Fifteen patients ranging from 25 to 59 years of age were studied. All underwent abdominal operations. The average operating time was 2 hours and 42 minutes, and the mean anaesthetic time was 3 hours and 45 minutes. The type of operation and the ages of the patients are shown in Table I. In none of them was there any clinical evidence of endocrine disorder or impaired renal or hepatic function, nor had any received ACTH or corticosteroid compounds.

Each patient was premedicated with pentobarbitone 100 mg orally 1½ hours before the induction of anaesthesia, atropine 0.5 mg and meperidine 35 mg intramuscularly 1 hour prior to induction. Anaesthesia was induced at 8.30 a.m. with an inspired Ethrane concentration of 1.5 to 4.0 per cent delivered from a Fluotec Mark II Vaporizer, combined with nitrous oxide (2 L/min) and oxygen (2 L/min). After endotracheal intubation had been carried out following intravenous succinylcholine 40 mg, anaesthesia was maintained with Ethrane (1.5 to 3.5 per cent) in nitrous oxide (2 L/min) and oxygen (2 L/min). Tubocurarine 15 to 24 mg was injected as required in divided doses.

Ventilation was controlled or assisted intermittently throughout the procedure. A moderate depth of anaesthesia was maintained as judged by clinical criteria and based on physical signs including blood pressure, pulse rate, and somatic reflex responses to the surgical stimulation. Low molecular weight dextran 500 ml was infused throughout the procedure until blood loss exceeded 300 ml, when whole blood was transfused. Eight blood samples were obtained from each patient. (1) Immediately before induction of anaesthesia, (2) 15 minutes after induction of anaesthesia, (3) 30 minutes after the start of anaesthesia, (4) 15, 30, 60, and 120 minutes after the start of the operation, and (5) in the recovery room.

Three ml of venous blood was collected on each occasion into a heparinized syringe. One ml of plasma was used for cortisol assays according to the method of

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TABLE I
PATIENTS STUDIED AND OPERATIONS PERFORMED

Case no.	Age	Sex	Operation	Op. Time	Anaes. Time
1	25	F	Simple hysterectomy	1°25'	2°10'
2	59	M	Prostatectomy	2°00'	3°05'
3	25	M	Gastrectomy	2°05'	3°25'
4	42	F	Simple hysterectomy	1°55'	2°40'
5	46	F	Oophorectomy	2°10'	3°00'
6	39	M	Gastrectomy	2°00'	3°15'
7	39	F	Simple hysterectomy	2°40'	3°00'
8	47	F	ibid.	2°50'	5°00'
9	28	M	Cholecystectomy	3°45'	5°20'
10	39	F	Pyeloureterostomy	2°45'	3°55'
11	54	F	Cholecystectomy	5°50'	6°30'
12	49	F	Simple hysterectomy	2°05'	2°50'
13	57	F	ibid.	2°25'	3°10'
14	36	F	ibid.	4°20'	5°50'
15	45	F	It nephrectomy	2°20'	3°10'
Mean				2°42'	3°45'

TABLE II
ARTERIAL BLOOD GAS ANALYSES DURING ETHRANE-NITROUS OXIDE ANESTHESIA

Time	PO ₂	PCO ₂	pH	B.E.
Pre-ind.	76.2 ± 6.1	36 ± 2.4	7.38 ± 0.2	+1.3 ± 1.8
Anaes. 15 min.	203.8 ± 13.2	33 ± 3.3	7.41 ± 0.1	+1.6 ± 0.9
Anaes. 30 min.	253.4 ± 14.6	32 ± 2.6	7.42 ± 0.2	+1.8 ± 0.3
Op. 30 min.	238.1 ± 24.2	33 ± 3.2	7.51 ± 0.1	-0.5 ± 1.3
Op. 1 h.	201.6 ± 39.3	32 ± 2.5	7.42 ± 0.2	-1.3 ± 0.8
Recovery	121.9 ± 19.8	34 ± 3.8	7.40 ± 0.1	+1.6 ± 1.8

(±S.E.)

Rudd *et al.*⁷ PaO₂, PaCO₂, pH, and base excess were determined in arterial blood at 37° C by means of an Astrup ultra-micro analyzer with a Severinghaus electrode. No evidence of hypoxia or hypercarbia was found during the procedure (Table II).

RESULTS

The mean preanaesthetic plasma level of cortisol in the morning immediately prior to induction of anaesthesia was $10.4 \pm 0.6 \mu\text{g}$ per 100 ml. It decreased significantly to $8.6 \mu\text{g}$ per 100 ml following 30 minutes of anaesthesia. Then, however, the mean plasma level of cortisol rose significantly to $16.1 \mu\text{g}$ up 30 minutes after the start of the operation. The elevation continues for 2 hours thereafter with a peak level ($26.1 \mu\text{g}$) in the recovery room when the patient was awake and had recovered from anaesthesia (Figure 1).

DISCUSSION

Ethrane is a newly introduced halogenated ether, with properties not dissimilar to halothane. It appears superior to halothane however in the following respects: muscle relaxation can be achieved, induction and recovery are rapid, arterial blood pressure is stable and no effects on hepatic function have been demonstrated.^{5-8,10}

Ethrane anaesthesia alone for 30 minutes caused a reduction of plasma cortisol

level in our study, but this was slight, amounting only to $1.8 \mu\text{g}$ per 100 ml. After the start of operation it gradually and significantly increased, as occurs also with other anaesthetic agents.¹⁻⁴

Clinically Éthrane resembles halothane, but its effect on adrenocortical function in man is comparable to that of methoxyflurane² rather than to halothane.¹ It is interesting to note that the chemical structure of Éthrane also ($\text{CHF}_2\text{-O-CF}_2\text{CHFCl}$) is similar to that of methoxyflurane ($\text{CH}_3\text{-O-CF}_3\text{CHCl}_2$).

Dobkin *et al.*⁵ have reported that plasma cortisol levels in patients receiving Éthrane anaesthesia for 30 minutes rose from a control level of $31.6 \pm 1.3 \mu\text{g}$ per 100 ml to $69.7 \pm 2.7 \mu\text{g}$ per 100 ml. Their results differ from our study, and it is difficult to speculate on the reason for this discrepancy. The method of analysis of plasma cortisol levels and the method of administering Éthrane might in part contribute to the difference between the two reports.

Hypoxia or hypercarbia have been reported to stimulate the adrenal cortex to judge from adrenocortical secretion¹¹ or from peripheral cortisol levels¹² in anaesthetized dogs. As shown in Table II, neither hypoxia nor hypercarbia occurred during Éthrane anaesthesia in our study. Therefore these factors do not enter into our study.

Éthrane itself appears to be a non-stressing agent in terms of adrenocortical function in man. Therefore, this seems to be the anaesthetic of choice for patients with hyperadrenocortical function such as occurs in Cushing's syndrome.

SUMMARY

The present study was undertaken to investigate the effect of Éthrane anaesthesia on adrenocortical function reflected by plasma cortisol levels in 15 surgical patients.

TABLE III
PLASMA CORTISOL LEVELS DURING ETHRANE-N₂O ANAESTHESIA AND SURGERY (μ g/100 ml)

Case	Pre-ind.	Anaes. 15	30	Op. 15	30	60	120	R.R.
1	10.5	12.5	13.5	19.5	26.0	28.0	—	29.0
2	14.8	13.7	12.1	11.0	12.8	19.0	20.0	22.1
3	14.0	14.0	11.5	—	23.0	20.0	—	16.5
4	11.3	10.0	8.7	10.0	14.5	17.0	18.4	23.0
5	7.0	10.0	5.5	9.5	11.5	14.5	—	15.5
6	11.0	10.0	11.0	18.0	10.0	22.5	28.0	32.0
7	12.0	8.5	7.5	9.0	18.0	18.0	21.0	30.0
8	7.5	8.5	8.0	8.0	16.0	19.0	22.0	25.0
9	10.0	8.5	8.5	10.5	16.5	18.0	20.0	24.0
10	10.5	8.5	8.0	8.5	15.0	17.0	20.0	25.0
11	8.5	7.5	6.0	17.0	21.5	24.0	28.5	43.5
12	12.5	9.0	8.0	8.0	14.0	17.0	21.0	23.0
13	8.0	7.5	6.0	5.0	13.5	20.5	24.0	33.0
14	9.5	8.0	7.0	14.5	23.0	24.0	26.0	29.0
15	9.5	7.5	7.0	8.0	6.5	12.5	14.5	20.5
Mean	10.4	9.6	8.6	11.2	16.1	19.4	22.0	26.1
S.E.	0.6	0.5	0.6	1.1	1.3	1.0	1.1	1.8
P		0.085	0.002	0.567	0.001	0.001	0.001	0.001

Ethrane anaesthesia alone for 30 minutes significantly but slightly decreased plasma cortisol level. However, it could not block the adrenocortical stimulation caused by surgical operation.

RÉSUMÉ

La présente étude a été entreprise pour rechercher les effets de l'anesthésie à l'éthrane sur la fonction adrénocorticale reflétée par les niveaux de cortisol plasmatique chez 15 opérés. L'anesthésie à l'éthrane seul durant 30 minutes a diminué le niveau de cortisol plasmatique de façon évidente quoique légère. Cependant, cela ne pouvait pas bloquer la stimulation adrénocorticale causée par l'opération chirurgicale.

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