THE COAGULATION-FIBRINOLYSIS SYSTEM IN MAN DURING ETHRANE® ANAESTHESIA AND SURGERY

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INTRODUCTION

THE CIRCULATORY AND RESPIRATORY RESPONSES to Ethrane® have been studied since 1966, but the effect of Ethrane® on the coagulation-fibrinolysis system has not been published. The present study was undertaken to determine whether an haemorrhagic tendency may occur during surgical operations under Ethrane® anaesthesia in man.

METHODS

1. *Subjects*

Twenty patients, undergoing gynaecological operations (mainly panhysterectomy), were the subjects of the present study. The pre-operative bleeding time, coagulation time, hepatic function and renal function were normal. None of these patients had any severe anaemia and none received a haemostatic agent. The diagnosis, type of surgery, duration of operation and anaesthesia, volume of haemorrhage, and volume of intravenous fluids administered are shown in Table I.

2. *Anaesthetic Method*

Premedication, given in the usual manner, consisted of pentobarbitone 100 mg, meperidine 35 mg, and atropine 0.5 mg.

After control blood sampling, the subject started to inhale 2 litres of oxygen and 4 litres of nitrous oxide combined with Ethrane®. Concentration of Ethrane® was increased from 0.5 per cent to 2.5 per cent by opening a Fluotec® vapourizer one notch of calibration after every two or three respirations. After loss of consciousness tracheal intubation was performed with relaxation provided by injection of succinylcholine chloride 40 mg. Anaesthesia was maintained with 2 litres of oxygen and 2 litres of nitrous oxide. The Fluotec® vapourizer was kept at between 1.0 per cent and 2.0 per cent for the maintenance of anaesthesia. Curare was administered when needed. Five hundred ml of low molecular weight dextran was used throughout the procedure. Anaesthesia was maintained for 30 minutes before beginning the operation and during that period a maximum of 100 ml of low molecular dextran was used. When bleeding exceeded 400 ml, whole blood was transfused.

3. *Time and Method of Blood Sampling*

Blood was withdrawn five times; immediately before induction of anaesthesia at 8.30 a.m. (which served as a control), 30 minutes after the start of anaesthesia,

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TABLE I
SURGICAL OPERATIONS PERFORMED

Case	Age	Surgical Procedure	Operating Time	Anaesthesia Time	Blood Loss	Blood Transfusion	Fluid
1	41	Panhysterectomy	2°50'	4°15'	345	0	1000
2	41	Panhysterectomy	4°00'	6°15'	437	400	1000
3	44	Panhysterectomy	3°35'	4°15'	530	600	1000
4	47	Panhysterectomy	5°37'	7°25'	970	800	1500
5	46	Panhysterectomy	4°22'	5°07'	914	1000	1000
6	48	Panhysterectomy	3°00'	4°05'	240	0	1000
7	39	Panhysterectomy	2°55'	4°05'	400	200	1500
8	46	Panhysterectomy	4°30'	5°15'	440	400	1500
9	50	Panhysterectomy	3°10'	3°45'	430	200	1000
10	38	Exploratory laparotomy	2°20'	3°05'	180	0	500
11	60	Panhysterectomy	3°00'	3°40'	320	0	1500
12	40	Panhysterectomy	3°18'	4°20'	262	0	1000
13	44	Panhysterectomy	3°15'	4°29'	160	0	1000
14	40	Hysterectomy	2°15'	3°01'	261	0	1000
15	41	Panhysterectomy	3°10'	4°00'	940	800	1000
16	47	Panhysterectomy	3°40'	4°25'	350	0	1000
17	38	Panhysterectomy	3°20'	4°25'	700	680	1000
18	66	Panhysterectomy	2°15'	3°00'	538	400	1000
19	35	Hysterectomy	2°08'	3°00'	244	0	1000
20	51	Colpoperineorrhaphy	1°35'	2°52'	136	0	1000
Mean			3°12'	4°14'	439	274	1075

° = hours. ' = minutes.

30 minutes and 1 hour after beginning the operation, and in the recovery room when the patient was fully awake. The blood samples were taken through an indwelling polyvinyl catheter into a disposable plastic syringe which contained a mixture of nine volumes of venous blood and one volume of 3.8 per cent sodium citrate. The plasma was subjected to the determinations tabulated below and paired Student *t*-tests were employed for statistical analysis.

4. Methods of Determinations

- (a) Platelet count (Brecher-Cronkete method)
- (b) Thrombin time (seconds) (Hougie method)
- (c) Partial thromboplastin time (seconds)
- (d) Prothrombin time (seconds) (Quick one-stage method)
- (e) Plasminogen ($\times 10^{-3}$ P.U.) (modified Maki method)
- (f) Fibrinogen (mg/100 ml) (Maki modification of the Rathoff-Menzie method)
- (g) Euglobulin clot lysis time (minutes).

RESULTS

1. Platelet Count

The platelet count immediately before the induction of anaesthesia averaged $23.5 \pm 1.14 \times 10^4/\text{mm}^3$ ($\pm$ S.E.). It was $21.0 \pm 1.07 \times 10^4/\text{mm}^3$ 30 minutes after the start of anaesthesia, 23.1 ± 1.4 , 19.9 ± 1.63 one hour after starting the operation and $20.6 \pm 1.0 \times 10^4/\text{mm}^3$ in the recovery room. Thus, all were within the normal range and no appreciable variation was noted (Table II).

TABLE II
PLATELET COUNT DURING ETHRANE® ANAESTHESIA AND SURGICAL OPERATION

Case	Platelet Count ($\times 10^4/\text{mm}^3$)				
	Preincubation	Anaesthesia (30')	Operation (30')	Operation (1°)	Recovery Room
3	16.8	17.2	16.2	15.0	21.0
4	20.0	22.0	20.6	23.2	25.0
5	22.2	15.0	17.6	15.0	16.0
6	24.6	25.0	21.8	17.0	11.0
7	33.4	20.0	34.0	30.0	23.0
8	15.6	19.4	—	18.2	17.4
9	22.0	23.4	—	12.8	21.4
10	28.8	28.6	29.8	18.6	24.2
11	20.0	19.6	26.0	20.8	19.0
12	23.6	24.0	22.0	28.0	19.0
13	29.7	19.6	—	—	16.2
14	22.6	12.4	14.0	18.0	16.0
15	18.2	26.6	24.0	17.4	20.0
17	24.2	18.0	24.0	27.4	24.0
18	26.4	19.6	27.2	18.6	17.2
20	28.4	26.2	22.6	28.8	28.2
Mean	23.5	21.0	23.1	19.9	20.6
S.E.	1.19	1.07	1.46	1.63	1.00
p		N.S.	N.S.	N.S.	N.S.

' = minutes. ° = hours. N.S. = not significant.

2. Coagulation System

(a) *Thrombin time*. Prior to the induction of anaesthesia, the thrombin time averaged 12.2 ± 0.40 seconds ($\pm$ S.E.). It was 12.6 ± 0.56 seconds 30 minutes after the beginning of anaesthesia and thus within the normal range. During the operation (30 minutes after incision) it showed some prolongation (14.5 ± 1.25 seconds), which was not a significant difference. In the recovery room, the thrombin time was 12.7 ± 0.56 seconds, which is a normal level (Table III).

(b) *Prothrombin time*. Prothrombin time was 13.7 ± 0.38 seconds ($\pm$ S.E.) before the induction of anaesthesia. It was slightly, but significantly, decreased to 13.3 ± 0.41 seconds 30 minutes after the start of anaesthesia and to 13.2 ± 0.36 seconds 30 minutes after the beginning of operation. Prothrombin times did not change and were within normal range during the operations (13.2 ± 13.6 seconds) and in the recovery room (13.6 seconds) (Table IV).

(c) *Partial thromboplastin time (P.T.T.)*. Partial thromboplastin time prior to the induction of anaesthesia was 60.0 ± 3.8 seconds ($\pm$ S.E.). It decreased insignificantly to 56.7 ± 3.06 seconds 30 minutes after the start of anaesthesia but before the operation. P.T.T. further decreased significantly (49.6 ± 1.94 seconds, $p < 0.001$) 30 minutes after the start of operation and returned to the preinduction level (60.3 ± 9.3 seconds) one hour after the start of operation. In the recovery room, however, it was again reduced significantly to 47.1 ± 2.0 seconds ($p < 0.01$) (Table V).

3. Results on the Fibrinolysis System

(a) Plasma plasminogen level before the induction of anaesthesia was $16.3 \pm$

TABLE III
THROMBIN TIME DURING ÉTHRANE® ANAESTHESIA AND SURGICAL OPERATION

Case	Thrombin Time (seconds)				
	Preinduction	Anaesthesia (30')	Operation (30')	Operation (1°)	Recovery Room
1	10.6	19.2	15.4	16.0	14.8
2	11.2	11.0	10.4	10.8	10.0
3	14.6	14.2	24.8	13.2	12.4
7	10.6	11.4	10.8	9.8	10.8
8	11.6	13.2	14.4	11.0	13.0
9	14.6	14.2	24.8	13.2	12.4
10	11.4	12.2	16.0	13.6	15.0
11	11.8	11.6	10.2	12.2	10.0
12	15.2	12.4	14.4	12.6	13.2
13	13.6	15.4	11.4	—	—
14	12.2	10.4	10.2	16.0	10.0
15	10.6	11.8	16.8	12.0	18.0
16	14.8	14.8	11.8	—	13.6
17	12.2	11.4	11.0	11.4	12.0
18	12.8	13.4	12.2	14.4	15.6
19	14.2	13.6	13.8	15.0	13.4
20	13.2	12.0	12.6	13.6	11.4
Mean	12.2	12.6	14.5	14.3	12.7
S.E.	0.40	0.56	1.25	2.00	0.56
p		N.S.	N.S.	N.S.	N.S.

' = minutes. ° = hours. N.S. = not significant.

TABLE IV
PROTHROMBIN TIME DURING ÉTHRANE® ANAESTHESIA AND SURGICAL OPERATION

Case	Prothrombin Time (seconds)				
	Preinduction	Anaesthesia (30')	Operation (30')	Operation (1°)	Recovery Room
1	12.2	11.0	11.8	10.6	11.2
2	10.6	11.2	9.8	10.8	10.0
3	14.6	14.4	15.2	13.4	14.0
6	12.8	11.4	11.8	11.6	12.0
7	12.6	12.0	12.0	11.6	12.4
8	17.6	16.8	15.6	18.4	17.0
9	14.6	14.4	15.2	13.4	14.0
10	11.8	11.4	13.4	12.8	17.2
11	14.4	15.0	13.8	14.2	12.6
12	13.2	12.2	12.8	12.0	12.6
13	13.4	14.0	13.6	—	12.8
14	15.6	15.0	14.0	15.4	14.0
15	15.0	14.8	15.0	14.2	14.2
16	15.0	15.6	14.2	17.8	17.6
17	12.2	11.4	11.0	11.4	12.0
18	12.8	13.4	12.2	14.4	15.6
19	14.2	13.6	13.8	15.0	13.4
20	13.2	12.0	12.6	13.6	11.4
Mean	13.7	13.3	13.2	13.6	13.6
S.E.	0.38	0.41	0.36	0.53	0.49
p		0.05	0.05	N.S.	N.S.

' = minutes. ° = hours. N.S. = not significant.

TABLE V
PARTIAL THROMBOBLASTIN TIME DURING ÉTHRANE® ANAESTHESIA AND SURGICAL OPERATION

Case	Partial Thromboplastin Time (seconds)				
	Preinduction	Anaesthesia (30')	Operation (30')	Operation (1°)	Recovery Room
3	70.2	64.2	58.8	54.6	41.4
6	56.0	50.0	45.0	44.0	38.6
7	52.0	58.0	51.0	44.4	47.6
8	100.0	84.0	63.0	67.0	68.0
9	70.2	54.2	58.8	54.6	41.4
10	40.8	40.2	35.4	35.0	47.0
11	69.4	84.0	48.0	43.0	39.0
12	58.0	49.0	49.0	37.6	41.6
13	65.0	58.8	50.0	—	63.4
14	47.2	54.0	40.8	42.0	44.0
15	57.0	46.0	47.0	47.4	46.0
16	45.6	49.0	46.0	108.0	45.2
17	62.0	50.0	52.8	42.6	44.4
18	33.0	43.0	41.8	46.4	58.0
19	54.8	57.4	43.6	57.4	42.0
20	78.8	55.6	63.0	3.0	46.2
Mean	60.0	56.7	49.6	60.3	47.1
S.E.	3.89	3.06	1.94	9.36	2.08
P		N.S.	0.001	N.S.	0.01

' = minutes. ° = hours. N.S. = not significant.

0.80×10^{-3} P.U. ($\pm$ S.E.). It decreased significantly ($p < 0.001$) 30 minutes and one hour after the start of operation. In the recovery room it was still significantly decreased to $13.2 \pm 0.68 \times 10^{-3}$ P.U. ($p < 0.001$) (Table VI).

(b) The fibrinogen level before the induction of anaesthesia was 248.7 ± 14.56 mg/100 ml ($\pm$ S.E.). It decreased to 224.6 ± 17.43 mg/100 ml 30 minutes after the induction of anaesthesia, this being within normal range but exhibiting a statistically significant decline ($p < 0.05$). The fibrinogen level decreased gradually and significantly ($p < 0.05$) during operation, being 216.3 ± 19.35 mg/100 ml and 198.1 ± 19.08 mg/100 ml 30 minutes and one hour after the start of operation, respectively. It was further reduced to 181.8 ± 24.96 mg/100 ml in the recovery room ($p < 0.03$) (Table VII).

(c) The euglobulin clot lysis time was 226.7 ± 7.9 minutes ($\pm$ S.E.) before the induction of anaesthesia. It decreased significantly up to 197.4 ± 15.84 minutes 30 minutes after the start of anaesthesia. It decreased significantly ($p < 0.001$) to 101.1 ± 18.03 and 101.0 ± 17.04 minutes, respectively, 30 minutes and one hour after the start of operation, but increased to 191.7 ± 16.86 minutes in the recovery room, exhibiting the tendency of returning to the control value (Table VIII).

DISCUSSION

We administered Éthrane® anaesthesia for 20 gynaecological operations (mostly panhysterectomy) performed by the same surgeons, and examined the coagulation-fibrinolysis system during anaesthesia alone and during operation. The platelets were counted and the coagulation system was evaluated by thrombin time, pro-

TABLE VI
PLASMA PLASMINOGEN LEVELS DURING ETHRANE® ANAESTHESIA AND SURGICAL OPERATION

Case	Plasma Plasminogen Levels ($\times 10^{-3}$ P.U.)				
	Preinduction	Anaesthesia (30')	Operation (30')	Operation (1°)	Recovery Room
1	19.6	17.5	16.4	13.7	16.0
2	25.4	14.2	16.0	14.6	14.2
3	16.1	16.4	15.7	16.3	15.0
4	19.0	16.2	16.2	17.9	15.9
5	12.7	—	11.1	9.7	10.6
6	12.4	11.6	12.1	11.0	8.9
7	16.2	13.7	12.9	11.5	14.6
8	17.0	11.7	12.6	11.8	13.8
9	13.9	12.8	9.1	11.1	11.8
10	19.4	13.5	15.6	16.3	14.3
11	22.2	18.5	18.4	17.1	19.9
12	17.0	15.6	13.0	13.1	12.4
13	13.5	11.8	11.8	8.9	10.3
14	16.1	10.0	10.8	8.2	16.3
15	14.9	7.7	8.0	10.5	8.2
16	11.8	13.1	9.9	9.0	12.4
17	10.0	9.4	12.6	13.5	9.0
18	15.1	12.1	14.3	11.3	11.4
19	17.8	17.8	18.8	15.6	18.0
20	15.1	11.8	15.8	12.9	11.8
Mean	16.3	13.4	13.6	12.7	13.2
S.E.	0.80	0.67	0.66	0.63	0.68
0		0.01	0.001	0.001	0.001

' = minutes. ° = hours.

TABLE VII
PLASMA FIBRINOGEN LEVELS DURING ETHRANE® ANAESTHESIA AND SURGICAL OPERATION

Case	Plasma Fibrinogen Levels (mg/100 ml)				
	Preinduction	Anaesthesia (30')	Operation (30')	Operation (1°)	Recovery Room
1	226	184	152	140	106
2	212	130	142	84	—
3	260	352	386	416	322
4	410	360	398	290	426
6	328	311	315	298	253
7	270	329	279	214	230
8	228	153	140	177	210
9	210	168	127	142	120
10	245	192	156	202	—
11	351	279	250	194	253
12	227	214	155	153	91
13	172	177	179	—	106
15	214	163	163	187	110
16	227	186	212	246	191
17	163	144	158	91	42
18	227	217	296	168	73
19	200	180	163	147	130
20	306	304	222	220	246
Mean	248.7	224.6	216.3	198.1	181.8
S.E.	14.56	17.43	19.59	19.08	24.96
p		0.05	0.05	0.05	0.03

' = minutes. ° = hours.

TABLE VIII
EUGLOBULIN CLOT LYSIS TIME DURING ETHRANE® ANAESTHESIA AND SURGICAL OPERATION

Case	Euglobulin Clot Lysis Time (minutes)				
	Preinduction	Anaesthesia (30')	Operation (30')	Operation (1°)	Recovery Room
1	240	60	240	60	180
2	240	30	240	120	240
3	240	240	30	90	30
5	240	240	30	120	30
6	240	240	210	240	240
7	240	240	90	60	240
8	240	240	180	210	240
9	240	240	90	120	240
10	240	240	60	90	240
11	240	240	120	240	240
12	240	240	30	30	90
13	150	150	30	30	150
14	240	240	30	30	270
15	120	90	30	30	180
16	210	120	60	60	240
17	240	180	120	60	240
18	240	240	30	30	—
19	240	240	60	60	150
20	—	240	240	240	240
Mean	226.7	197.4	101.1	101.1	191.7
S.E.	7.90	15.84	18.03	17.04	16.86
P		N.S.	0.001	0.001	N.S.

' = minutes. ° = hours. N.S. = not significant.

thrombin time and partial thromboplastin time (P.T.T.). They were maintained practically within normal range. Plasminogen and euglobulin clot lysis times decreased significantly during Ethrane® anaesthesia alone for 30 minutes, and a further reduction was noted during the surgical operation. The fibrinogen level also tended to decrease. These findings suggest that Ethrane® anaesthesia and surgical operation accelerated the activity of the fibrinolytic system in man. The elucidation of this accelerated mechanism is beyond the scope of the present study. Administration of low molecular dextran, 1000 ml, was not found to cause any significant effect on the coagulation and fibrinolysis system in man.¹

We have observed acceleration, both in the coagulation and fibrinolysis systems, under halothane anaesthesia, thereby maintaining a balanced haemostatic mechanism.² Vanderveen *et al.*³ found mild disturbance in the coagulation system and prolonged bleeding time only during hypothermia. No difference was found in the blood coagulation factors by other methods of anaesthesia or with other anaesthetics. They observed a slight prolongation in the bleeding time and a decline in capillary resistance. Pison *et al.*⁴ found that the surgical operations increased fibrinolytic activity significantly. Dillon⁵ reported that the volume of bleeding during surgical operations under Ethrane® anaesthesia, was as normal as in other ordinary surgical operations.

The haemorrhagic diathesis is considered to be induced by abnormalities, platelets, blood vessels, coagulation, and fibrinolysis. The coagulation and fibrinolysis systems are collectively designated as the coagulation-fibrinolysis system. Under normal conditions there is constantly a dynamic equilibrium between the coagu-

lation and the fibrinolysis systems. When the equilibrium is upset by various stresses including surgery, anaesthesia, shock, anoxia, a variety of disturbances are produced. When the coagulation system is predominant, thrombus may be formed. Conversely, if the fibrinolytic system is predominant oozing may result in severe haemorrhage.⁶

Éthrane® anaesthesia showed a tendency to accelerated plasmin activity and decreased fibrinogen level. This might be interpreted as setting the stage for the development of a haemorrhagic tendency but in fact the changes are not so extensive as to warrant such an interpretation. It may be suggested that both anaesthesia and surgical operation are conducive to acceleration of coagulation and fibrinolysis, but, the haemostatic mechanism tends to keep a balance between coagulation and fibrinolysis and to be in equilibrium.

It is common knowledge that a haemorrhagic tendency becomes overt when the factors participating in the haemostatic mechanism are reduced to less than 20 per cent of normal. Therefore, although Éthrane® anaesthesia causes increased fibrinolysis and decreases fibrinogen level, unless the haemostatic mechanisms have been abnormal before operation no decline below the borderline levels can be observed. However, it should be kept in mind that Éthrane® seems to cause more fibrinolysis and a lower level of fibrinogen than is the case with other anaesthetics.² The possible need for an antiplasmin agent during operation should also be considered.

SUMMARY

The coagulation-fibrinolysis system was studied during Éthrane® anaesthesia and gynaecological operations in 20 patients.

No particular change was noted in the platelet counts, which remained within the normal range. In the coagulation system, no appreciable change was observed except for the partial thromboplastin time (P.T.T.) which was significantly shortened, both 30 minutes after the start of operation and in the recovery room when the patient had completely awakened from the anaesthesia.

In the fibrinolytic system, the plasminogen level and the fibrinogen level declined significantly.

It is considered that the fibrinolytic system is prominently accelerated under Éthrane® anaesthesia, but the haemostatic mechanism works in such a manner that bleeding is controlled. However, Éthrane® anaesthesia should be avoided or pre-operative administration of an antiplasminic agent recommended for patients with an abnormal haemostatic mechanism.

RÉSUMÉ

1. Le système coagulation-fibrinolyse a été étudié chez 20 patientes au cours d'interventions gynécologiques, sous anesthésie à l'Éthrane®.
2. Aucune modification particulière ne fut trouvée dans la numération plaquettaire qui est demeurée dans les limites normales. Le coagulogramme n'a pas été modifié de façon appréciable sauf le temps de thromboplastine partiel (P.T.T.) qui

était diminué de façon significative, ceci après 30 minutes de chirurgie et après l'éveil complet.

3. Pour ce qui est du système fibrinolytique, les taux de plasminogène et de fibrinogène étaient diminués de façon significative; le fibrinogène en particulier était abaissé de façon marquée.
4. Nous considérons que sous anesthésie à l'Ethrane, le système fibrinolytique est accéléré, mais que les mécanismes hémostatiques agissent de telle façon que l'hémorragie est contrôlée.

Cependant, chez les patients présentant des troubles de l'hémostase, on devrait éviter l'anesthésie à l'Ethrane à moins de leur administrer un agent antifibrinolytique avant l'intervention.

REFERENCES

1. OYAMA, T. Effect of low molecular weight dextran on coagulative-fibrinolytic system in man (to be published).
2. OYAMA, T., TAKICUCHI, M., KIMURA, K., & MAKI, M. Effect of fluothane anesthesia on coagulative-fibrinolytic system. *Jap. J. Anesthesiol.* 16: 686-692 (1967).
3. VENDERVEEN, J. L., MCGOVERN, J. J., BUNKER, J. P., & GOLDSTEIN, R. Effect of anesthesia on hemostatic mechanism in man. *Anesthesiology* 23: 92-100 (1962).
4. PISON, J., BOYAN, C. P., & CLIFFTON, E. E. Fibrinolytic activity in patients during operation. *J.A.M.A.* 191: 1026-1027 (1965).
5. DILLON, J. B., LEBOWITZ, M. H., & BLITT, C. D. Clinical investigation of compound 347 (Ethrane®). *Anesth. Analg.* 49: 1-10 (1970).
6. RODERIQUE, E. M. & WYNANDS, J. E. Blood coagulation and hemostasis. A review. *Canad. Anaesth. Soc. J.* 14: 129-151 (1967).