CORRELATION OF CONCENTRATIONS OF ETHER IN ARTERIAL BLOOD WITH ELECTRO-ENCEPHALOGRAPHIC PATTERNS OCCURRING DURING ETHER-OXYGEN AND DURING NITROUS OXIDE, OXYGEN AND ETHER ANESTHESIA OF HUMAN SURGICAL PATIENTS *

ALBERT FAULCONER, JR., M.D.

Rochester, Minnesota

Received for publication March 28, 1952

THE classification of electro-encephalographic patterns occurring during anesthesia with ether, and with nitrous oxide, oxygen and ether described in a previous publication (1), has proved to be useful. Seven levels were described, representing progressive changes during anesthesia of increasing depth from loss of consciousness to respiratory arrest (fig. 1). Correlation of these pattern changes with the commonly accepted signs by which depth of anesthesia is estimated clinically has proved to be inconclusive. The transient and somewhat inconstant nature of the clinical signs, and the variations in their interpretation

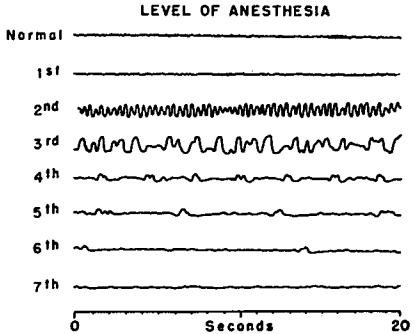

FIG. 1. A classification of electro-encephalographic pattern changes during increasing depth of ether-oxygen or nitrous oxide, oxygen and ether anesthesia of human beings. The first and second patterns occur during induction. Patterns 3, 4 and 5 occur during light, moderate and deep surgical anesthesia. Patterns 6 and 7 are seen during excessively deep anesthesia.

* From the Section of Anesthesiology and Intravenous Therapy, Mayo Clinic, Rochester, Minnesota.

by different individuals, render this approach uncertain. As a part of some unrelated studies done in collaboration with other investigators (2), many observations of concentrations of ether in arterial blood and, when present, concentrations of nitrous oxide in arterial blood are available. These data are, in every instance, associated with simultaneously recorded electro-encephalographic patterns. This report is of a study of the correlation between the electro-encephalographic level and the concentration of ether in arterial blood under various conditions relative to time and presence of nitrous oxide.

MATERIAL AND METHODS

The data reported here are derived from observations on 31 patients who were undergoing abdominal surgical operations (table 1). There were 11 females and 20 males. The females averaged approximately 54½ years in age, with a range of 28 to 77 years. The males averaged approximately 53½ years in age, with a range of 26 to 68 years. The average duration of anesthesia was approximately 105 minutes, with a range of from 47 to 280 minutes. Concentrations of ether were determined on 228 arterial samples drawn from these patients at intervals during the period of anesthesia. When nitrous oxide was used to supplement ether, the concentration of nitrous oxide in the blood was determined simultaneously with the concentration of ether.

The analysis of blood gas was accomplished by a mass spectrometric technic, the details of which are in preparation for publication (3, 4).

Interpretation of the electro-encephalographic pattern with a designation of level according to the classification outlined above was made by a single trained technician in the laboratory subsequent to the surgical operation concerned, and without her knowing the simultaneous concentration of blood ether.

RESULTS

The 228 observations were arbitrarily divided into the following groups (footnote to table 2):

Group 1—Those in which no nitrous oxide was present in the sample of blood (86 observations).

Group 2—Those in which the concentration of nitrous oxide in the sample of blood was less than 10 mg. per 100 cc. of blood (40 observations).

Group 3—Those in which the concentration of nitrous oxide was in excess of 10 mg. per 100 cc. of blood (102 observations).

The correlation between the concentration of ether in arterial blood and the electro-encephalographic level for 225 observations, regardless of the presence or absence of nitrous oxide, is indicated in figure 2. Levels 6 and 7 have been omitted because these data comprised only 2 and 1 observations respectively (table 3). It will be seen that the

TABLE 1

SUMMARY OF CASES*

Patient	Sex	Age, yrs.	Wt., lb.	Hb. % or Gm.	Minutes of Anesthesia†	Agent	Operation
1	M	36	141	8.5	120	N_2O–O_2–E	Transverse colostomy, subtotal colectomy
2	M	59	138	13.5	101	N_2O–O_2–E	Partial gastrectomy and partial gastroenterostomy
3	F	54	150	11.7	67	N_2O–O_2–E	Exploration, laparotomy
4	M	60	125	90.0	86	N_2O–O_2–E	Anterior resection, large bowel colocolostomy
5	F	55	144	11.6	130	N_2O–O_2–E	Anterior resection
6	M	40	158	12.8	56	N_2O–O_2–E	Cholecystectomy
7	M	61	132	13.0	88	N_2O–O_2–E	Bilateral herniorrhaphy
8	M	57	216	11.8	65	Ind(Pent)‡N_2O–O_2–E	Anterior resection of bowel and colostomy
9	M	60	154	12.7	47	N_2O–O_2–E	Exploratory laparotomy
10	M	58	236	12.4	52	Ind(N_2O)–O_2–E	Sigmoidotomy with excision of polyp
11	F	58	132	12.4	60	N_2O–O_2–E	Cholecystectomy
12	F	58	130	12.9	123	N_2O–O_2–E	Removal retroperitoneal chondroma
13	F	65	146	13.2	158	Ind(N_2O)–O_2–E	Removal carcinoma ampulla of Vater
14	M	68	155	13.0	95	Ind(N_2O)–O_2–E	Repair ventral hernia (left)
15	F	36	142	11.7	67	Ind(N_2O)–O_2–E	Abdominal hysterectomy; right salpingectomy
16	M	59	147	15.4	125	N_2O–O_2–E	Repair hernia and cholecystectomy
17	M	54	166		47	Ind(Pent)N_2O–O_2–E	Transcolonic sigmoid polyp removed
18	M	60	138	15.2	92	N_2O–O_2–E	Anterior resection
19	M	63	194	15.2	98	Ind(Pent)–O_2–E	Sigmoidal resection
20	F	77	175	16.4	72	Ind(Pent)–O_2–E	Anterior resection
21	M	37	149	12.8	186	N_2O–O_2–E	Ileostomy and total colectomy
22	F	28	151	13.6	66	N_2O–O_2–E	Cholecystectomy
23	M	54		16.0	97	N_2O–O_2–E	Excision jejunal diverticulum
24	M	45	192	12.8	280	N_2O–O_2–E	Whipple operation
25	M	65	182	14.8	110	N_2O–O_2–E	Cholecystectomy; appendectomy
26	F	57	137	11.5	52	N_2O–O_2–E	Pancreatic and retroperitoneal lesion, exploration
27	F	58	138	13.8	159	N_2O–O_2–E	Transverse colostomy
28	M	61	120	14.4	143	N_2O–O_2–E	Partial gastrectomy; posterior pulp
29	M	26	140	12.2	129	N_2O–O_2–E	Resection of terminal ileum, cecum and appendix; repair of postoperative ventral hernia
30	F	56	120	11.6	109	N_2O–O_2–E	Anterior resection
31	M	49		87.0	173	N_2O–O_2–E	Gastric resection

* Premedication was routine in all cases: nembutal grain 1½ (0.1 Gm.); morphine grain ¼ (0.01 Gm.); atropine grain 1/150 (0.00043 Gm.).

† Total time, 3,247 minutes; average time, 105 minutes.

‡ Ind = induction; Pent = pentothal; E = ether. The agent named in parentheses after the abbreviation "Ind" was used for induction only.

means of the values representing the concentration of blood ether for each of the five levels designated, suggest a remarkably high index of correlation. These means range from 52 mg. of ether per 100 cc. of blood at electro-encephalographic level 1 to 120 mg. per 100 cc. of blood

TABLE 2

CONCENTRATION OF ETHER IN ARTERIAL BLOOD AT DIFFERENT ELECTRO-ENCEPHALOGRAPHIC LEVELS IN PRESENCE OR ABSENCE OF NITROUS OXIDE: 228 OBSERVATIONS ON 31 PATIENTS

Electro-encephalographic Level and Concentration of Nitrous Oxide	Observations, number	Patients, number	Mean, mg. ether per 100 cc. blood	Standard Deviation	Standard Error of Mean
EEG level 1 (all cases)					
0 N_2O	4	4	63.0	22.2	12.8
− N_2O	6	1	49.0	18.4	8.3
+ N_2O	1	1	12.0		
EEG level 2					
0 N_2O	6	4	78.0	11.8	4.9
− N_2O	10	4	55.0	8.7	2.9
+ N_2O	6	4	59.0	38.2	17.1
EEG level 3					
0 N_2O	12	6	98.0	25.3	7.6
− N_2O	16	6	73.0	19.5	5.0
+ N_2O	20	8	84.0	16.3	3.7
EEG level 4 (all cases)					
0 N_2O	42	15	113.0	27.4	4.3
− N_2O	4	3	113.0	10.0	5.75
+ N_2O	61	17	97.0	24.0	3.1
EEG level 5					
0 N_2O	20	9	127.0	27.2	6.2
− N_2O	4	2	133.0	4.03	2.3
+ N_2O	13	6	106.0	20.1	6.0
EEG level 6					
0 N_2O	2	2	147.0		
EEG level 7					
+ N_2O	1	1	17.0		

Group 1, 0 N_2O = no N_2O present in blood; 86 observations.
Group 2, − N_2O = less than 10 mg. per 100 cc. of blood; 40 observations.
Group 3, + N_2O = more than 10 mg. per 100 cc. of blood; 102 observations.

TABLE 3

CONCENTRATIONS OF ETHER IN ARTERIAL BLOOD AT DIFFERENT ELECTRO-ENCEPHALOGRAPHIC LEVELS, DISREGARDING PRESENCE OR ABSENCE OF NITROUS OXIDE: 228 OBSERVATIONS ON 31 PATIENTS

Electro-encephalographic Level	Observations, number	Patients, number	Mean, mg. ether per 100 cc. blood	Standard Deviation	Standard Error of Mean
1	11	6	52	23.9	7.56
2	22	12	60	26.0	4.47
3	48	18	84	21.2	3.1
4	107	29	103	22.8	2.2
5	37	16	120	27.3	4.55
6	2	2	198–147		
7	1	1	17		

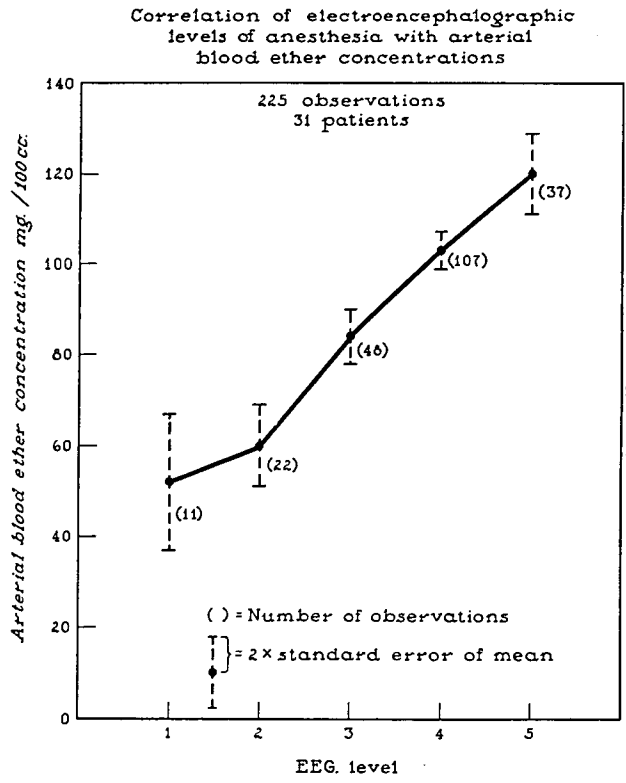

FIG. 2. The average concentration of ether in arterial blood required to produce the electro-encephalographic patterns indicated in figure 1. These averages include all observations, both with and without supplementary nitrous oxide. Premedication in every instance consisted of morphine sulfate grain ⅙ (0.01 gm.) and atropine sulfate grain 1/150 (0.00043 Gm.).

at electro-encephalographic level 5 in what is almost a straight line relationship on the graph (fig. 2).

Observations designated as those of group 1 in which nitrous oxide was not found in the blood (table 2), revealed an equally high index of correlation between the electro-encephalographic level and the mean concentration of ether in the arterial blood, varying from 63 mg. per 100 cc. at level 1 to 127 mg. per 100 cc. at level 5 (fig. 3). In the same

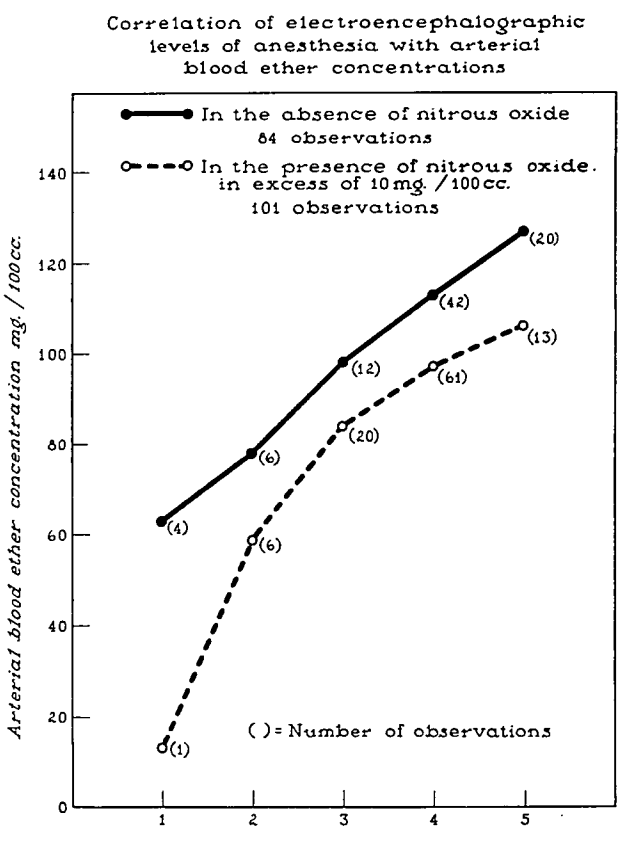

FIG. 3. The average concentration of ether in arterial blood required to produce the first five electro-encephalographic patterns shown in figure 1 in the absence of nitrous oxide (solid line) and when nitrous oxide also was present in the blood in excess of 10 mg. per 100 cc. (dotted line). The differences between the means indicated for electro-encephalographic levels 4 and 5 are statistically significant to a high degree.

figure are represented the observations designated as those of group 2; that is, those in which the concentration of nitrous oxide in the blood was in excess of 10 mg. per 100 cc. This line also reveals a high index of correlation although it is displaced somewhat below the line repre-

senting observations of group 1. Considered separately, statistically significant differences exist between the mean concentration of ether in the arterial blood, represented by points on the two lines at electro-encephalographic level 4 and again at level 5. These differences are significant to the 0.001 and 0.015 levels, respectively.

TABLE 4

CONCENTRATIONS OF ETHER IN ARTERIAL BLOOD AT DIFFERENT ELECTRO-ENCEPHALOGRAPHIC LEVELS, IN ABSENCE OF NITROUS OXIDE, BEFORE AND AFTER 45 MINUTES OF ANESTHESIA HAD ELAPSED: 80 OBSERVATIONS

Electro-encephalographic Level and Time after Beginning of Anesthesia	Observations, number	Patients, number	Mean, mg. ether per 100 cc. blood	Standard Deviation	Standard Error of Mean
Level 2					
Less than 45 min.	1				
More than 45 min.	5	4	102	50.2	25.1
Level 3					
Less than 45 min.	4	4	108	25.6	14.7
More than 45 min.	8	4	93	20.0	7.6
Level 4					
Less than 45 min.	20	15	106	29.3	6.7
More than 45 min.	22	10	123	23.2	4.9
Level 5					
Less than 45 min.	5	5	143	17.1	8.6
More than 45 min.	15	5	121	29.3	7.8

Again the observations were arbitrarily divided into two categories as follows:

Category 1—Those made before forty-five minutes of anesthesia had elapsed.

Category 2—Those made after forty-five minutes of anesthesia had elapsed (table 4).

Observations included were made in the absence of nitrous oxide. A statistically significant difference was not observed between these two categories.

COMMENT

These observations are presented as evidence that the classification of electro-encephalographic patterns used in this study is a valid indication of relative concentrations of arterial ether in human beings who are undergoing anesthesia with ether-oxygen and with nitrous oxide, oxygen and ether. It is of interest to note that there were many occasions when elements of two of the electro-encephalographic patterns were present simultaneously. In such instances the deeper (higher number) of the two was arbitrarily designated. It should be pointed out that from patient to patient, a marked degree of variability existed

in single observations of the concentration of ether in the blood at any one electro-encephalographic level. This is reflected in the large standard deviation shown in the accompanying tables. The meaning of this variability is obscure, although it probably is a manifestation of individual variation in tolerance for the drug. In referring to figure 3 and to table 2 it is apparent that a difference exists in the concentration of ether in arterial blood which is required to achieve any electro-encephalographic level from 1 to 5 inclusive, depending on whether nitrous oxide in concentrations in excess of 10 mg. per 100 cc. is simultaneously present in the blood or whether no nitrous oxide is present. A lower concentration of ether produces a given electro-encephalographic level if nitrous oxide also is present than if ether alone is the agent by which the change is wrought. The difference is significant to a degree verging on certainty. Therefore, it may be said that nitrous oxide in concentrations in excess of 10 mg. per 100 cc. of arterial blood reduces the concentration of ether in arterial blood required to produce a given electro-encephalographic level of anesthesia.

It is suggested that the method of analysis used in the compilation of data in figure 3 may be useful for solving similar pharmacologic problems. For example, the value of certain premedicants in reducing the dosage of the principal narcotic agents used to achieve a given electro-encephalographic level might be studied by this method.

SUMMARY

Electro-encephalographic patterns observed during increasing depth of anesthesia with ether-oxygen and with nitrous oxide, oxygen and ether were correlated with concentrations of ether in the arterial blood.

Almost a straight line correlation was revealed in 225 observations on 31 patients undergoing ether anesthesia with and without nitrous oxide when the means of the concentrations of blood ether observed at each electro-encephalographic level were plotted against the electro-encephalographic levels. The points on the correlation graph ranged from a mean concentration of ether in the arterial blood of 52 mg. per 100 cc. at electro-encephalographic level 1 to a mean of 120 mg. per 100 cc. at electro-encephalographic level 5.

A lower concentration of ether was required to produce each of the electro-encephalographic levels studied when nitrous oxide was present in the arterial blood in excess of 10 mg. per 100 cc. than when no nitrous oxide was present. This difference was shown to be statistically significant to a high degree for the observations made during electro-encephalographic levels 4 and 5.

It was suggested that this method of analysis is adaptable to the quantitative study of the contribution of each of two narcotic agents when used simultaneously, provided that a significant change in electro-

encephalographic pattern, subject to classification, is produced by the agents considered.

No significant difference could be determined between the means of concentration of ether in arterial blood required to produce specific electro-encephalographic levels in the absence of nitrous oxide, whether the observations were made earlier than 45 minutes after the beginning of anesthesia or later than 45 minutes after the beginning of anesthesia.

ACKNOWLEDGMENTS

The author is grateful to Miss Rosemarie Hnefliger for her diligence in compiling and checking the tables shown and for her time and effort in reading the electro-encephalographic tracings and assessing the levels revealed. The data presented herein include observations made as a part of the thesis work of Drs. R. A. E. Devloo, D. E. Soltero, J. S. Hattox and R. T. Patrick.

REFERENCES

1. Courtin, R. F.; Bickford, R. G., and Faulconer, Albert, Jr.: Classification and Significance of Electro-encephalographic Patterns Produced by Nitrous Oxide-ether Anesthesia During Surgical Operations, Proc. Staff Meet., Mayo Clin. **25**: 197–206 (Apr. 12) 1950.
2. Devloo, R. A. E.; Soltero, D. E.; Patrick, R. T.; Faulconer, Albert, Jr.; Bickford, R. G., and Saari, John: Unpublished data.
3. Jones, C. S.; Saari, John; Devloo, R. A. E.; Faulconer, Albert, Jr., and Blades, E. : Unpublished data.
4. Hattox, J. S.; Saari, John, and Faulconer, Albert, Jr.: Unpublished data.

(*Continued from page 360*)

Course No.	*Title*	*Instructor*
T11	"Development of Endotracheal and Endobronchial Methods of Anesthesia"	Ivan Magill, M.D.
F41	"The Role of the Anesthetist in the Prevention of Hemorrhage (Methonium Comp.)"	Ivan Magill, M.D.
W12	"Intravenous Procaine Therapy"	Stevens J. Martin, M.D.
F19–F49	"Dental Anesthesia"	Kenneth C. McCarthy, M.D.
F27–F57	"Transsacral Anesthesia"	Charles F. McCuskey, M.D.
F39–F69	"Anesthesia for Thoracic Surgery"	William O. McQuiston, M.D.
F17–F47	"Regional Anesthesia for Head and Neck"	Daniel C. Moore, M.D.
F16	"Carbon Dioxide in Anesthesia"	Lucien E. Morris, M.D.
W38–T17	"Stellate and Lumbar Sympathetic Ganglion Blocks"	Louis R. Orkin, M.D.
W27	"Cardiac Arrhythmias and Their Control During Anesthesia"	Sidney, Orth, M.D.
W57	"Effects of Anesthetics on Hepatic and Renal Function"	Sidney Orth, M.D.
W48	"Cardiac Resuscitation"	E. M. Papper, M.D.
F32	"Anesthetic Management for Caesarian Section"	Robert L. Patterson, M.D.
F62	"Obstetric Amnesia and Analgesia"	Robert L. Patterson, M.D.
W13–T33	"Bronchoscopy for the Anesthesiologist"	William E. Pembleton, M.D.
T24	"Intrathecal Vasoconstrictors"	J. K. Potter, M.D.
T12	"Tracheal Intubation with Topical Anesthesia"	Donald F. Proctor, M.D.
W28–W58	"Cutaneous Innervation"	Curt Richter, M.D.
F58	"Classic Spinal Anesthesia"	Henry S. Ruth, M.D.
W33–W63	"Manual Artificial Respiration"	Max S. Sadove, M.D.

(*Continued on page 373*)