EFFECT OF PREANESTHETIC MEDICATION ON ETHER CONTENT OF ARTERIAL BLOOD REQUIRED FOR SURGICAL ANESTHESIA

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PREANESTHETIC medication commonly is assumed to serve certain functions, including the establishment of a state of psychic tranquillity, elevation of the threshold for pain, the counteraction of undesirable side actions of the anesthetic agent, and the depression of reflex irritability of the central nervous system. This study is concerned with the last of these four functions.

Astute clinical observers have been convinced for many decades that some drugs administered prior to use of the primary anesthetic agent do, in fact, bear an important part of the burden of anesthesia (1, 2). However, results of attempts to measure this function have not been convincing. Robbins and associates (3) considered that use of morphine reduced the quantity of cyclopropane required to attain a given plane of anesthesia. Cohen and Beecher (4) were unable to find a significant reduction in the blood levels of cyclopropane or ether required for operation when morphine and atropine, pentobarbital and atropine, or atropine alone had been used in premedication. Potter and associates (5) were unable to find differences in the concentration of ether in venous blood of patients undergoing surgical procedures, regardless of whether or not the patient had been given morphine as part of the premedication. On the other hand, Turpeinen (6) concluded that premedication with morphine and scopolamine reduced the amount of ether in arterial blood required to produce general anesthesia.

In an attempt to make objective quantitative observations of the depression of reflex irritability induced by the preanesthesia medication that we have surveyed, two assumptions have been made. The first may be summarized as follows: If a drug or agency (for example, hypothermia) contributes significantly to depression of reflex irritability of the central nervous system, it is assumed that the mean concentration of a narcotic drug (ether in this case) in the arterial blood necessary to produce a given level of anesthesia will be less when the patient has been preconditioned with such an agent.

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The question can be resolved only when means are available for determining the depth of anesthesia and the concentration of ether in blood whose reliability and consistency are within the limits imposed by the differences that may be found. To these ends we have made our second assumption, namely that the electroencephalographic classification of the depth of anesthesia devised by Courtin and coworkers (7) is valid. To increase the reliability of this estimate, we have chosen "level 4" as a depth that has been associated with moderately deep surgical anesthesia in a large percentage of observations and that is easy to interpret on an electroencephalogram.

Method

The analyses for ether in the blood were made on a six-channel iodine pentoxide train, similar to that used by Haggard (8) as modified by one of us (Doerr). The validity of this method for the measurement of ether is shown in table 1, which reveals an over-all root mean square

TABLE 1

Validity of Method for Determination of Ether in Blood

Analyses	Known Concentration of Ether (mg./100 ml.)	Root Mean Square Error of Analyses (per cent)*
5	191	±3.2
4	121	±8.8
6	113	±3.5
6	102	±6.2
20	132	±10.5

* Mean error of the 41 analyses = ±7.8 per cent.

error of ± 7.8 per cent when the method was checked against five different known mixtures of blood and ether in 41 analyses. The analyses of known samples were done using one of the six channels available, in rotation, each time samples were analyzed. This method provided a continuing check on the validity of the analytic method. As a further check, a sample of venous blood was drawn from each patient prior to induction of anesthesia and was run with the experimental samples as a blank.

Assessment of the electroencephalographic level was made by one of us (Faulconer) without prior knowledge of the amount of ether in the patient's blood. If the electroencephalographic level was deemed to be either too "high" or too "low," the sample drawn at the time the record was obtained was not included in this study.

A total of 52 patients undergoing ether-oxygen anesthesia for major abdominal operations were observed. They were grouped as follows:

Group 1 (10 patients) received, hypodermically, 0.4 mg. of atropine sulfate about forty-five minutes before anesthesia. This group served as the controls.

Group 2 (7 patients) received, intravenously, 10 mg. of morphine sulfate and 0.4 mg. of atropine sulfate ten minutes before anesthesia.

Group 3 (8 patients) received intravenously 50 mg. of meperidine (Demerol) hydrochloride and 0.4 mg. of atropine sulfate thirty minutes before anesthesia.

Group 4 (7 patients) received intravenously 200 mg. of pentobarbital sodium approximately ten minutes before anesthesia.

Group 5 (7 patients) received intramuscularly 50 mg. of chlorpromazine diluted with 2 ml. of a 1 per cent solution of procaine hydrochloride one hour before anesthesia.

Group 6 (6 patients) received intravenously 2.5 mg. of levorphan (Levo-Dromoran, 3-hydroxy-*N*-methylmorphinan) tartrate plus 0.25 mg. of levallorphan ten minutes before anesthesia, preceded by a hypodermic injection of 0.4 mg. of atropine sulfate about thirty minutes before anesthesia.

TABLE 2

DATA IN GROUP 1: CONTROLS RECEIVING ATROPINE ONLY

Patient	Weight (pounds)	Age (years)	Sex	Hemoglobin (Gm./100 ml.)	Number of Analyses at EEG Level 4	Mean Concentration of Ether (mg./100 ml.)*
1	129	73	M	10.8	2	113
2	137	64	F	12.9	3	124
3	155	59	F	12.2	4	121
4	202	61	M	—	4	115
5	123	71	M	—	5	116
6	120	61	M	—	3	135
7	140	68	M	—	3	115
8	105	37	F	—	3	138
9	125	42	F	—	2	122
10	153	78	M	—	4	115

* Mean value of the 33 analyses = 121 ±2.6.

Group 7 (7 patients) received orally 1 Gm. of ethinamate (Valmid, 1-ethynylcyclohexyl carbamate) approximately one hour before anesthesia, followed by a hypodermic injection of 0.4 mg. of atropine sulfate about thirty minutes before anesthesia.

Anesthesia in each patient was induced by means of nitrous oxide and oxygen, after which ether was added to the mixture and the nitrous oxide was washed out as rapidly as possible. Mass spectrometric analysis of several samples of blood for the content of nitrous oxide revealed insignificant concentrations of nitrous oxide in the blood at the time samples were drawn for measurement of ether.

An attempt was made to maintain the patient at electroencephalographic level 4 throughout the procedure. Samples of arterial blood were drawn periodically in sealed syringes for subsequent analysis. The arterial concentration designated for each patient is the mean of the findings from these periodic samples.

Results

The results of these studies are summarized in tables 2 through 8 and in figure 1. The mean concentration of ether in the arterial blood of the control group of patients was 121 mg. per 100 ml. of blood (table 2). This is in good agreement with other studies (9). The mean con-

TABLE 3

Data in Group 2: Patients Receiving Morphine and Atropine

Patient	Weight (pounds)	Age (years)	Sex	Number of Analyses at EEG Level 4	Mean Concentration of Ether (mg./100 ml.)*
11	170	56	M	5	115
12	147	72	F	4	91
13	138	61	M	4	97
14	158	50	M	5	114
15	100	33	M	4	104
16	108	45	F	2	101
17	190	68	M	5	98

* Mean value of the 29 analyses = 103 ±3.4.

TABLE 4

Data in Group 3: Patients Receiving Meperidine (Demerol) and Atropine

Patient	Weight (pounds)	Age (years)	Sex	Hemoglobin (Gm./100 ml.)	Number of Analyses at EEG Level 4	Mean Concentration of Ether (mg./100 ml.)*
18	148	61	M	13.5	4	103
19	162	52	M	15.0	4	119
20	117	40	F	9.8	1	102
21	140	64	M	11.4	4	101
22	150	39	F	13.2	4	115
23	170	64	F	13.6	4	116
24	127	54	M	15.2	3	92
25	110	35	F	12.6	3	110

* Mean value of the 27 analyses = 107 ±3.5.

TABLE 5

Data in Group 4: Patients Receiving Pentobarbital

Patient	Weight (pounds)	Age (years)	Sex	Hemoglobin (Gm./100 ml.)	Number of Analyses at EEG Level 4	Mean Concentration of Ether (mg./100 ml.)*
26	160	64	M	15.2	3	77
27	143	60	F	12.6	2	100
28	141	52	M	16.1	4	80
29	230	61	M	10.8	4	96
30	154	49	M	13.2	4	99
31	164	54	M	11.7	4	80
32	116	70	F	10.9	4	85

* Mean value of the 25 analyses = 88 ±4.0.

TABLE 6

Data in Group 5: Patients Receiving Chlorpromazine

Patient	Weight (pounds)	Age (years)	Sex	Hemoglobin (Gm./100 ml.)	Number of Analyses at EEG Level 4	Mean Concentration of Ether (mg./100 ml.)*
33	125	50	F	12.7	3	112
34	123	48	F	11.8	3	104
35	163	60	F	11.3	4	101
36	163	61	F	12.0	1	101
37	167	49	M	15.2	4	98
38	110	46	F	13.4	4	102
39	175	42	F	11.8	4	133

* Mean value of these 23 analyses = 107 ±4.9.

TABLE 7

Data in Group 6: Patients Receiving Levo-dromoran, Levallorphan and Atropine

Patient	Weight (pounds)	Age (years)	Sex	Hemoglobin (Gm./100 ml.)	Number of Analyses at EEG Level 4	Mean Concentration of Ether (mg./100 ml.)*
40	—	54	M	12.7	2	121
41	167	43	M	16.4	3	120
42	185	39	M	13.0	3	123
43	216	54	M	13.9	4	120
44	162	52	M	11.8	5	123
45	196	46	M	15.7	3	123

* Mean value of these 20 analyses = 122 ±0.67.

TABLE 8

Data in Group 7: Patients Receiving Valmid and Atropine

Patient	Weight (pounds)	Age (years)	Sex	Hemoglobin (Gm./100 ml.)	Number of Analyses at EEG Level 4	Mean Concentration of Ether (mg./100 ml.)*
46	114	30	F	12.7	4	133
47	172	63	M	13.8	4	111
48	152	70	M	12.2	3	110
49	215	39	M	15.9	4	114
50	198	28	M	14.8	4	147
51	176	62	M	13.4	4	113
52	140	62	F	11.8	4	141

* Mean value of these 27 analyses = 124 ±6.2.

centrations of ether in patients given ethinamate as premedication or with the mixture of levorphan and levallorphan did not differ significantly from those of the control group. Patients given premedication of chlorpromazine, meperidine or morphine had significantly smaller mean concentrations of ether in the arterial blood at electroencephalographic level 4. The patients who received pentobarbital required a

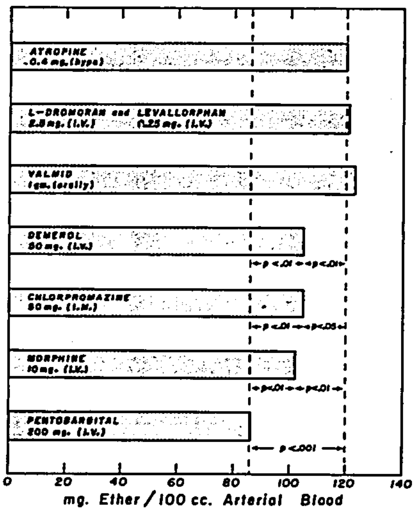

FIG. 1. Comparison of the mean concentrations of ether in arterial blood in patients anesthetized to electroencephalographic level 4 after premedication with various drugs.

mean concentration of ether in the arterial blood of only 88 mg. per 100 ml. to evoke electroencephalographic patterns of level 4.

COMMENT

All patients in this study were well anesthetized clinically for abdominal operations when the samples of blood were drawn and no patient was deemed to be excessively depressed. It should not be concluded that these findings represent the measure of the value of the agents studied as preanesthetic medication for human anesthesia.

These data merely indicate the probable value of these drugs in the doses used in fulfilling one of several functions of premedication. We hope that the methods described may prove to be useful in the hands of other workers.

SUMMARY

The content of ether was measured in the arterial blood of 52 patients undergoing ether anesthesia at the same moderately deep surgical level (electroencephalographic level 4).

Each of 7 groups of patients received different premedication.

Atropine alone was used in the first group, which served as a control. No significant reduction in the requirement for ether was noted in patients receiving premedication with ethinamate or a mixture of levorphan and levallorphan. Premedication with chlorpromazine, meperidine or morphine allowed level 4 of anesthesia to be attained with significantly smaller blood concentrations of ether. Use of pentobarbital for preanesthetic medication was associated with the smallest concentrations of ether at comparable levels of anesthesia.

The authors wish to acknowledge the technical assistance of Richard L. Bickford.

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