The Electroencephalogram as a Monitor of Arterial Blood Levels of Methoxyflurane

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The electroencephalogram (EEG) was monitored in 40 patients receiving methoxyflurane. Three anesthetic techniques were used depending on the inclusion or omission of thiopental for induction and nitrous oxide during maintenance. Arterial blood levels of methoxyflurane obtained when changes in the EEG occurred were measured by gas chromatography. With increasing depth of anesthesia four EEG stages were defined, three of which were correlated with blood levels of the agent. These stages showed the classical progression of initial fast activity followed by increasingly slow rhythm, high voltage activity and finally intermittent electrical suppression. Higher levels of methoxyflurane were necessary to produce successive EEG changes where first thiopental and then nitrous oxide was omitted from the anesthetic technique. A linear relationship between the level of methoxyflurane and the EEG stage of anesthesia was seen.

THE USE of the electroencephalograph (EEG) during anesthesia has been described by Faulconer and Bickford [1] and more recently by Marshall *et al.*[2] Although EEG patterns during methoxyflurane anesthesia have been described by a number of investigators [3-6] there has been only one attempt to correlate the findings with blood levels of the agent and in this only two blood levels were reported.[7] The present study was designed, therefore, to correlate EEG changes with arterial blood levels of methoxyflurane and to determine the extent to which the EEG might be of value as a monitor during anesthesia with this agent.

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Method

The subjects of this study were between 16 and 70 years of age, undergoing surgery other than intracranial or intrathoracic and free of disease other than that for which the operation was being done. They were divided into the following groups: *Group I*—In 20 patients, anesthesia was induced with thiopental (approximately 5 mg./kg. body weight) and maintained with nitrous oxide-oxygen (2:1) and methoxyflurane. *Group II*—In 10 patients, anesthesia was induced and maintained with nitrous oxide-oxygen and methoxyflurane. *Group III*—In 10 patients, anesthesia was induced with thiopental and maintained with oxygen and methoxyflurane.

In all groups, premedication consisted of atropine (0.4 to 0.6 mg.) or scopolamine (0.4 mg.) plus pentobarbital (75 to 100 mg.) and/or meperidine (50 to 100 mg.). In all subjects, intubation, facilitated by succinylcholine, was performed and ventilation was controlled throughout in an attempt to maintain the P_{CO_2} between 30 and 40 mm. of mercury. Methoxyflurane was vaporized either with a number 8 Heidbrink vaporizer or, in a few instance, with a Foregger Pentomatic vaporizer. Both depolarizing and nondepolarizing relaxants were used as indicated.

Fine needle electrodes were used as leads. A dual channel cardioencephalography * was used to record both EEG and ECG. Calibration of the machine was such that a 1 cm. deflection indicated 100 microvolts in the EEG tracing; paper speed was set at 2.5 cm. per second. Initially the electrodes were placed one inch apart over the frontal area of the dominant hemisphere. In a number of these cases interpretation of the tracings obtained

* Gilson Medical Electronics.

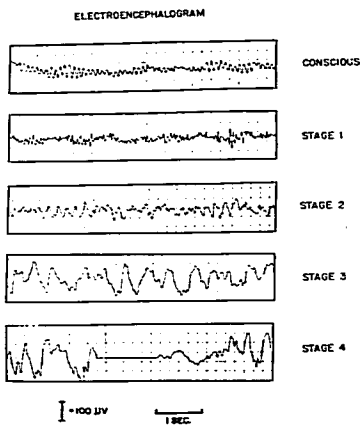

FIG. 1. Electroencephalographic changes during methoxyflurane anesthesia.

was difficult owing to low voltage either prior to or during anesthesia. These leads were therefore abandoned after ten cases and fronto-occipital leads substituted. An EEG was obtained immediately prior to the induction of anesthesia except where it was felt that this procedure would be distressing to the patient.

Following induction of anesthesia an indwelling needle was place in a brachial or radial artery and its patency maintained by a constant slow infusion of normal saline. Surgery was then allowed to commence.. Methoxyflurane concentrations were progressively increased at a rate determined by the response of the blood pressure. Whenever the blood pressure fell by more than 25 per cent of the preoperative value it was allowed to recover before there was any further increase in methoxyflurane concentration. If necessary, methoxyflurane was withdrawn and then introduced more gradually. If hypotension persisted or recurred, the study was abandoned. Specimens of blood were taken at 10 minute intervals and/or when a difference in EEG pattern appeared. Methoxyflurane levels were measured by gas chromatography [8] and CO_2 tensions with a modified Severinghaus electrode.† Blood pressure and pulse rate were recorded every 5 minutes and in most patients the electrocardiogram was also monitored.

Results

Thirty-two electroencephalograms were obtained before induction of anesthesia. Alpha wave activity (8 to 12 cycles per second) was seen with fronto-occipital leads and beta wave activity (24 to 28 cycles per second) was seen with frontal leads. During anesthesia both leads yielded tracings of similar rhythm but with frontal leads the voltage was commonly much lower. The voltages described refer to fronto-occipital leads.

After induction of anesthesia the EEG patterns in the first two groups could conveniently be divided into four stages (fig. 1). The administration of thiopental in Group I caused slowing associated with an increase in voltage. This effect was transitory and was rapidly replaced by the appearance of Stage 1. This was seen in all patients in Groups I and II and consisted of intermediate fast activity usually of 15 to 18 cycles per second and of 20 to 60 microvolts. Symmetrical waxing and waning of voltage in this stage led to the appearance of "spindling" in approximately half the patients. This stage was not due specifically to methoxyflurane and was seen prior to its introduction in a number of instances in Group I.

Stage 2 was heralded by the appearance of theta waves at the rate of 4 to 7 cycles per second with a voltage of 50 to 75 microvolts. Pure theta wave activity was unusual, a mixture of intermediate fast and theta waves being more characteristic of this stage. The average blood level at which stage 2 commenced was 11.25 mg./100 ml. with a range from 8.5 to 13.5 mg./100 ml. in Group I (table 1) and 14.0 mg./100 ml. with a range from 10.0 to 18.9 mg/100 ml. in Group II (table 2). This difference was statistically significant ($t‡ = 3.0$). Stage 2 was distinguished in 17 subjects in Group I and 9 in Group II. In the remaining 4 subjects in these groups, the first change to appear was that of Stage 3.

† Instrumentation Laboratories.
‡ Student's *t*.

TABLE 1. Electroencephalographic Stages and Average Blood Levels During Anesthesia with Thiopental, Nitrous Oxide, Oxygen and Methoxyflurane

Stage	Average Blood Level at First Appearance of Stage (mg./100 ml.)	Range of Blood Levels at First Appearance of Stage (mg./100 ml.)
2	11.25±1.8 (17 estimations)	8.5–13.5
3	16.4 ±2.9 (16 estimations)	12.5–20.0
4	21.5 ±3.1 (12 estimations)	17.5–26.0

TABLE 2. Electroencephalographic Stages and Average Blood Levels During Anesthesia with Nitrous Oxide, Oxygen and Methoxyflurane

Stage	Average Blood Level at First Appearance of Stage (mg./100 ml.)	Range of Blood Levels at First Appearance of Stage (mg./100 ml.)
2	14.0±3.58 (9 estimations)	10.0–18.9
3	20.2±2.67 (8 estimations)	17.9–22.5
4	26.8±2.76 (8 estimations)	21.0–30.5

The appearance of delta waves of 1 to 3 second marked the beginning of Stage 3. The voltage of these waves varied from 50 to 200 microvolts. Combinations of intermediate fast, theta and delta waves were commonly seen. The irregular nature of the delta waves plus the superimposition of faster activity produced a characteristically mixed tracing. The average blood level at which this stage appeared was 16.4 mg./100 ml. with a range from 12.5 to 20.0 mg./100 ml. in Group I (table 1) and 20.2 mg./100 ml. with a range from 17.9 mg./100 ml. to 22.5 mg./100 ml. in Group II (table 2). This difference was statistically significant ($t = 5.0$). As in Stage 2, pure rhythmic activity was uncommon. When such delta wave activity did occur it usually immediately preceded Stage 4. Stage 3 was distinguished in 16 subjects in Group I and 8 in Group II. In 2 subjects in Group I and in one in Group II there was a transition directly from Stage 2 to Stage 4 and in the remaining 3 subjects persistent hypotension occurred before the appearance of Stage 3.

Stage 4 was characterized by intermittent suppression of electrical activity (burst suppression). Activity between suppressions consisted of combinations of previously described patterns. The average blood level at which burst suppression was first seen was 21.5 mg./100 ml. with a range from 17.5 to 26.0 mg./100 ml. in Group I (table 1) and 26.8 mg./100 ml. with a range from 21.0 to 30.5 mg./100 ml. in Group II (table 2). This difference was statistically significant ($t = 6.5$). Total suppression of activity was never sought but was seen on two occasions, once in Group I with a blood level of 17.5 mg./100 ml. and once in Group II with a blood level of 41.0 mg./100 ml. In both these instances the patient's vital signs were within normal limits. Stage 4 was distinguished in 12 subjects in Group I and 8 in Group II. In the remaining 10 subjects persistent hypotension occurred before the appearance of this stage.

In Group III, Stage 1 (intermediate fast activity) appeared as in the other two groups However, Stage 2 (theta waves) could not be distinguished in this group and the first change seen was the appearance of delta waves (Stage 3). The average blood level at which this stage appeared was 26.3 mg./100 ml. with a range from 23.0 to 28.9 mg./100 ml. (table 3). This level was significantly different from the level of onset of Stage 3 in Groups I ($t = 12$) and II ($t = 6.7$). Stage 3 was seen in 8 subjects in this group. In one subject the first EEG change seen was that of Stage 4 and in

TABLE 3. Electroencephalographic Stages and Average Blood Levels During Anesthesia with Thiopental, Oxygen and Methoxyflurane

Stage	Average Blood Level at First Appearance of Stage (mg./100 ml.)	Range of Blood Levels at First Appearance of Stage (mg./100 ml.)
3	26.3±3.3 (8 estimations)	23.0–28.9
4	34.0±4.4 (6 estimations)	28.0–37.0

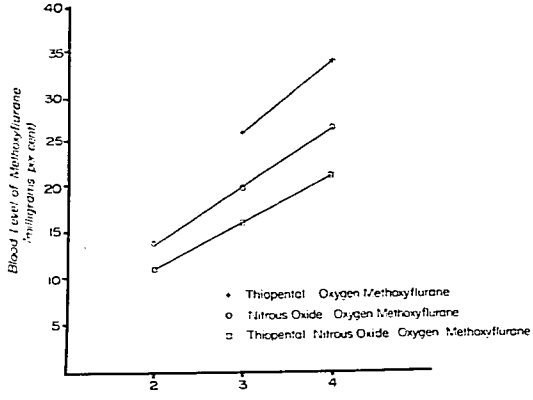

FIG. 2. Linear relationship between blood levels of methoxyflurane and successive electroencephalographic stages shown for nitrous oxide, oxygen, methoxyflurane anesthesia with and without thiopental induction.

the other persistent hypotension occurred before any EEG changes were seen. Burst suppression (Stage 4) appeared in this group at an average blood level of 34.0 mg./100 ml. with a range from 28.0 to 37.0 mg./100 ml. (table 3). This was significantly different from the level of onset of Stage 4 in Groups I ($t = 11.5$) and II ($t = 4.6$). In 4 subjects in this group persistent hypotension occurred before the appearance of Stage 4. Persistence of fast activity during Stages 3 and 4 was much more marked in this group than in the other two.

The average blood levels at the time of onset of Stages 2, 3 and 4 in Groups I and II and Stages 3 and 4 in Group III are shown in figure 2. Increasing blood levels of methoxyflurane were required to attain each stage as first thiopental and then nitrous oxide was omitted from the anesthetic technique. A linear relation may be seen between the blood levels at succeeding stages, with each technique.

Although hypotension (systolic blood pressure less than 75 per cent of preoperative level) was observed at some time in a number of patients, the EEG patterns described were all seen during normotensive states (systolic blood pressure within 25 per cent of preoperative level). The ECG was stable throughout except for two occasions on which a gradual shift of the pacemaker from the SA to the AV node occurred. A return to the SA node was seen as soon as the administration of methoxyflurane was reduced or discontinued.

Most of the patients were mildly hyperventilated as may be seen from the average P_{CO_2} determinations shown in table 4. The highest P_{CO_2} measured was 58 mm. of mercury. This occurred in a patient in Group I with a methoxyflurane blood level of 10.5 mg./100 ml. and a Stage 1 EEG. The lowest P_{CO_2} measured was 21 mm. of mercury. This occurred in a patient in Group III with a methoxyflurane blood level of 26.6 mg./100 ml. and a Stage 3 EEG. In both instances blood levels and EEG stages conformed to the other findings in this study where CO_2 tensions were closer to the desired range.

Discussion

Although specific EEG patterns have been described for various inhalational agents, basic similarities exist. Initially, anesthesia produces an increase in the rate of activity. With advancing depth there occurs a slowing in rate and increase in voltage followed by progressive suppression of electrical activity.

This effect was well demonstrated by methoxyflurane. However, there was a definite tendency for fast activity to persist into the deeper stages of anesthesia. This was particularly noticeable in the absence of nitrous oxide. Because of this persisent fast activity changes from one stage to another were not

as clearly defined as with ether.[3] Thus it was important to use the appearance of theta or delta waves or burst suppression as the main criteria of depth irrespective of the intermittent occurrence of fast activity. Generally, however, as each stage progressed, activity typical of the previous stage gradually diminished.

The EEG findings described here are similar to those of others.[3-7] Minor differences may be attributable to subdivision by other authors of the present Stage 1. Thus, the spindling that Campbell *et al.*[5] described in Stage 3 and Anderson *et al.*[4] described in Stage 2 of their respective classifications was seen in Stage 1 of the present work. Subsequent patterns in both publications [4, 5] were similar to those of this report. Intermediate fast activity (Stage 1) was seen on occasion in Group I of the present study, prior to the introduction of methoxyflurane. We have also seen this type of activity during light halothane anesthesia and during narcotic supplemented nitrous oxide-oxygen anesthesia. These findings suggest that Stage 1 may represent a non-specific response to light general anesthesia.

Nishioka [7] who used only oxygen and methoxyflurane in some of his subjects described 3 to 6 cycle, 40 to 60 microvolt activity at a blood level of 35.0 mg./100 ml. and burst suppression at 40.0 mg./100 ml. In Group III of the present study where thiopental was used in addition to oxygen and methoxyflurane, average blood levels of 26.3 mg./100 ml. and 34.0 mg./100 ml. were seen in Stages 3 and 4, respectively. The EEG patterns of these stages were the ones most similar to Nishioka's findings. Had thiopental been omitted in this group the blood levels necessary to attain these stages would presumably have been higher (compare Groups I and II in the present study) and more comparable to those reported by Nishioka.

TABLE 4. Mean P_{CO_2} (mm. hg) Levels at Different Electroencephalographic Stages During Anesthesia with: Thiopental, Nitrous Oxide, Oxygen and Methoxyflurane (Group I); Nitrous Oxide, Oxygen and Methoxyflurane (Group II) and Thiopental, Oxygen and Methoxyflurane (Group III)

	Mean P_{CO_2} (mm. Hg) Levels		
	Stage 2	Stage 3	Stage 4
Group I	34.8±4.4	35.9±5.5	34.3±3.1
Group II	33.5±4.3	32.4±3.8	35.0±4.2
Group III	—	32.9±3.1	30.8±4.4

The present study was divided into three groups in order to provide information for the most common clinical technique using methoxyflurane (Group I) and for two less common variations (Groups II and III). Although the use of methoxyflurane-oxygen alone would have been of interest, this was not done because of the prolonged induction time associated with this technique.

Similar EEG patterns in the three groups were associated with significantly different blood levels of methoxyflurane. Thus blood levels of any anesthetic agent may only be correlated with EEG changes within the framework of the entire anesthetic technique.

Courtin *et al.* (9) described modification of EEG level 1 and delay in the appearance of EEG level 2 with nitrous oxide, oxygen, ether anesthesia after an induction dose of thiopental. However, no blood levels of ether were reported. In the present study a single dose of thiopental reduced the amount of methoxyflurane necessary to produce EEG changes. This prolonged effect of thiopental has not previously been reported. Prolonged enhancement of the cardiovascular depressant effect of methoxyflurane, by thiopental, was suggested by the higher incidence of hypotension in Groups I and III compared to Group II. However, these differences were not statistically significant.

The effect of nitrous oxide in reducing the amount of methoxyflurane necessary to produce each EEG change is comparable to that described by Faulconer [10] for ether. The absence of Stage 2 in the group which did not receive nitrous oxide is comparable to the findings reported by Courtin [11] for trichlorethylene. He described a stage of theta wave activity during nitrous oxide-oxygen, trichlorethylene anesthesia which reverted to fast activity on withdrawal of the nitrous oxide. Theta wave activity due to nitrous oxide has also been described by Pearcy *et al.*[12] It would appear that the theta wave

activity seen in this study was more representative of light planes of nitrous oxide, oxygen, methoxyflurane anesthesia than of methoxyflurane itself.

The linear relation demonstrated between the blood levels of methoxyflurane necessary to produce the various stages of EEG activity has also been shown for ether[10] and cyclopropane.[13]

The use of muscle relaxants and controlled respirations in this study made it difficult to correlate EEG findings and depth of anesthesia. Commonly, adequate anesthesia, with or without adequate relaxation, was seen in Stage 2 and, after prolonged administration, in Stage 1. However, there were instances of inadequate relaxation despite early burst suppression. Although surgery was in progress during these studies, reversion to an earlier EEG stage was never seen in response to surgical stimulation. This also suggests that anesthesia was adequate by the time Stage 2 was reached.

In the present study when induction was carried out swiftly, without the need to pause because of hypotension, high blood levels were generally recorded at the commencement of any given EEG pattern. Where hypotension slowed induction there was more time available for blood-brain equilibration and each EEG pattern tended to occur at a lower level. The reverse situation obtained after methoxyflurane was withdrawn and a given EEG pattern persisted at blood levels of methoxyflurane below those reported here for the first appearance of each stage. These variations in blood levels associated with variations in induction time may reflect the lag between the occurrence of EEG changes and clinical signs of anesthesia reported by Galla *et al.*[12]

The effect of hypercarbia in deepening the EEG level during ether anesthesia without coincident increase in the blood ether concentrations has been shown.[15] With the highest P_{CO_2} seen in this study (58 mm. of mercury) the EEG findings (Stage 1) were compatible with the methoxyflurane level (10.5 mg./100 ml.) for Group I. Hypocarbia may be associated with high voltage slow wave activity.[16] With the lowest P_{CO_2} seen in this study (21 mm. of mercury) the EEG findings (Stage 3) were compatible with the methoxyflurane level (26.6 mg./100 ml) for Group III. Most CO_2 tensions in the study were within the low normal range (table 4). These findings suggest that CO_2 tension was not a significant factor in this study.

The results of this study demonstrated that it was not possible to assess arterial blood level from any isolated EEG pattern. Other factors to be taken into consideration were speed of induction, duration of anesthesia and whether or not methoxyflurane was being administered at the time the tracing was made. With this information, however, it became possible to make a reasonable estimate of blood level at any given time, provided that Stage 2, 3, or 4 had been encountered.

Summary

A study was carried out in 40 patients to evaluate the EEG as a monitor during methoxyflurane anesthesia. Four patterns were described depending on the presence or absence of theta waves, delta waves or burst suppression. A linear relationship was shown between the average blood levels at which successive EEG patterns appeared. The effect of thiopental and nitrous oxide in reducing the amount of methoxyflurane necessary to produce these patterns was shown.

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Nervous System

MONAMINE OXIDASE INHIBITORS The duration of action of norepinephrine released from cytoplasmic storage granules of neurones upon neuronal stimulation is largely limited by uptake again into nerve cytoplasm and storage granules and to a much lesser extent by diffusion away from the nerve ending and enzymatic destruction by catechol-O-methyl transferase. The chief function of monamine oxidase present in the mitochondria of adrenergic nerve endings may be to metabolize cytoplasmic norepinephrine that leaks from storage granules and escapes re-uptake. Monamine oxidase inhibitors cause an increase in neuronal stores of norepinephrine, but the mechanisms for disposing of norepinephrine released as a neurotransmitter or injected into the circulation are not disturbed other than by the limitation on tissue uptake imposed by the greater tissue stores. In experiments with human volunteers taking monamine oxidase inhibitors it was found, as expected, that injected norepinephrine is not potentiated. Ephedrine acts by releasing stored norepinephrine and since these stores are increased by monamine oxidase inhibitors the action of ephedrine is substantially potentiated. Phenylephrine acts chiefly directly on receptors and only to a small extent by release of stored norepinephrine and little potentiation occurs after intravenous administration, as expected. Substantial amounts of monamine oxidase are found in the intestine and liver and since phenylephrine acts as a substrate for monamine oxidase, administration of an inhibitor must be expected to increase absorption of phenylephrine. In 3 subjects, amounts of phenylephrine which barely caused blood pressure rise when given orally before monamine oxidase inhibitors, caused such dramatic blood pressure rise after inhibitors that the administration of the alpha blocking agent, phentolamine, was necessary. The inhibitors used in this study were phenelzine and tranylcypromine. *(Elis, J., and others: Modification by Monoamine Oxidase Inhibitors of the Effect of Some Sympathomimetics of Blood Pressure, Brit. Med. J. 1: 75 (April) 1967.)*