Graefe's Arch Clin Exp Ophthalmol (1986) 224:473–476

Graefe's Archive
for Clinical and Experimental
Ophthalmology
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Electroretinogram as a possible monitor of anesthetic depth

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Abstract. The effects of volatile anesthetics, i.e., methoxyflurane, halothane and enflurane, on the electroretinogram (ERG) were studied in 15 albino rabbits. The ERG was analyzed in terms of the a-wave, and the first oscillatory component (01) in the b-wave. The 01 peak latency showed a significant dose-related prolongation when anesthetic end-tidal concentrations were in excess of 0.8 minimum alveolar concentration (MAC). One MAC, a measure of anesthetic potency, is the end-tidal concentration of an anesthetic at 1 atmosphere that induces immobility in 50% of animals against a noxious stimulus. The amplitudes of the a-wave and the 01 decreased in dose-dependent manners, but their changes were less striking than those of the 01 latency. The peak latency of the a-wave remained unchanged. We conclude that the 01 peak latency is a useful monitor of the depth of inhalational anesthesia.

Introduction

The electroretinogram (ERG) is of great value in the clinical examination of ophthalmological diseases and also in the investigation of visual science or neurophysiology. The ERG, furthermore, could be a useful intraoperative monitor of anesthetic depth and hypoxia since it has been reported to be sensitive to anesthetics, hypoxia, and hypercapnea (Raitta et al. 1979, 1982; Niemeyer et al. 1982). While the visual evoked potentials (VEP) have been reported to be altered at clinical levels of inhalational anesthesia (Uhl et al. 1980; Raitta et al. 1979, 1982), little use has been made of these techniques for monitoring the depth of anesthesia. The reasons may include patient-to-patient variability, the inability to detect readily changes in anesthetic depth, variability of response to different anesthetic agents and the difficulty of interpretation.

In the present study, we have examined the ERG as a simpler and more reliable means of assessing the anesthetic depth universally.

Materials and methods

Animal preparation

Fifteen albino rabbits were used. An earlobe vein was cannulated for fluid infusion. After the animal was anesthetized with 3% enflurane in oxygen, tracheostomy was done and a femoral artery was cannulated for arterial pressure monitoring and blood-gas sampling. The rabbit was paralyzed with continuous infusion of succinylcholine chloride (10 mg/kg per h) and artificially ventilated with oxygen to maintain $PaCO_2$ at 35 ± 4 (mean $\pm$ SD) mmHg. End-tidal concentrations of carbon dioxide and anesthetics were continuously monitored with a calibrated mass spectrometer (R-MC, Shimazu, Kyoto, Japan). Esophageal temperature was controlled at $40.3° \pm 0.4°$ (mean $\pm$ SD) C with a warming blanket.

ERG recordings

Mydriasis was carried out with a mixture of 0.5% phenylephrine HCl and 0.5% tropicamide. Platinum ring electrodes mounted on a scleral contact lens were applied to the cornea. The contact lens had an artificial pupil size of 10 mm in diameter. The ERG responses were recorded with a preamplifier, a memory oscilloscope and an X–Y plotter (AD-624M, ATAC 210 and RW11S, Nihon Koden Co, Tokyo, Japan). Signal averaging was not performed. The frequency characteristic of the preamplifier was in the range of 100–10,000 Hz (−3dB). Stimulus light was obtained from a stroboscopic xenon lamp (2 J) equipped in an ERG photic stimulator (SLS-4100, Nihon Koden Co, Tokyo, Japan). The distance between the lamp and the eye to be tested was 15 cm. Both the rabbit and the xenon lamp were covered by black vinyl coverings to facilitate dim adaptation of the eye.

After the animal had been prepared, the ERG was recorded at 3-min intervals throughout the experiment. A steady state was obtained within 30 min, as confirmed by the reproducibility of ERG recordings. Three successive ERG recordings 60 min after initiation of photic stimulation served as control (unanesthetized) measurements.

The effects of methoxyflurane, halothane, and enflurane on the ERG were studied in 15 rabbits, divided into three groups of 5 each. Anesthesia was induced with high concentrations of each anesthetic, 0.75% methoxyflurane, 3% halothane, or 4% enflurane. The initial inspiratory concentrations were maintained for 5 min. Anesthetic gas was delivered with oxygen from commercial vaporizers (Pentec Mark 2, Fluotec Mark 3 and Enfluratec, Cyprane Ltd, Keighloy, England). Inspiratory anesthetic concentrations were reduced from the initial levels to obtain end-tidal concentrations of 0.2% and 0.1% for methoxyflurane, 1.4% and 0.7% for halothane, and 3%, 2%, and 1% for enflurane.

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Table 1. Peak latencies and amplitudes (mean±SD) of the a-wave and first oscillatory component (01) and mean arterial pressure at different anesthetic concentrations

End-tidal % (MAC)	Peak Latency (ms)		Amplitude (μV)		Mean arterial pressure (torr)
	a-wave	01	a-wave	01	
Methoxyflurane ($n=5$)					
0% (0)	4.0±0.4	13.3±0.6	116±34	12.6±4.8	87±11
0.1% (0.4)	4.0±0.4	13.2±0.6	114±35	13.2±2.3	79±12
0.2% (0.9)	4.1±0.4	17.1±2.1[b]	97±38	10.9±3.5	63±12[a]
Halothane ($n=5$)					
0% (0)	3.9±0.2	13.6±0.9	114±29	13.3±6.1	89±12
0.7% (0.8)	4.0±0.3	15.7±2.0[a]	113±35	12.3±7.5	81±13
1.4% (1.6)	4.2±0.3	21.6±3.0[c]	102±31	6.6±5.2[a]	66±13[a]
Enflurane ($n=5$)					
0% (0)	3.9±0.2	13.7±0.9	112±15	14.2±4.2	85±10
1.0% (0.5)	3.8±0.2	13.7±0.9	108±23	13.5±5.9	76±12
2.0% (0.9)	3.9±0.3	16.3±1.4[a]	103±25	12.0±4.7	76±13
3.0% (1.4)	3.9±0.3	20.4±3.2[b]	99±26	8.8±4.5	70±13

[a] $P<0.05$, [b] $P<0.01$, [c] $P<0.001$; significant from control

Each end-tidal concentration was held constant for at least 30 min. ERG waveforms at 3-min intervals changed during the first 12 min but remained unchanged during the latter 18 min. Thereafter, three successive ERG waveforms were recorded at 3-min intervals and superimposed together on a single sheet of paper.

In order to compare the effect at the same anesthetic depth, anesthetic potency was expressed in terms of MAC multiples. One MAC is the minimum alveolar concentration of an anesthetic at one atmosphere that produces immobility in 50% of animals exposed to a noxious stimulus (Eger 1974). To convert end-tidal concentrations into MAC multiples, each end-tidal concentration was divided by known MAC values as follows: methoxyflurane 0.23%, halothane 0.87% and enflurane 2.2%.

ERG analysis

A typical control ERG waveform in this study contained three components, that is, the a-wave, the b-wave, and the oscillatory components (wavelets) superimposed on the b-wave. The peak latency was defined as the time difference between the photic stimulus and the peak. The amplitude of the a-wave was defined as the voltage difference between the baseline and the maximal deflection of the a-wave. The amplitude of the first oscillatory component (01) was defined as the difference between the 01 peak and the b-wave. The b-wave was defined as a curve which traveled through the midpoints between the maxima and minima of oscillatory sinusoids. Both the amplitude and peak latency of the b-wave were omitted from measurement because its shape was modified by the filter and drawn by hand. Data were statistically analyzed by Student's *t*-test.

The compressed array of the ERG

After obtaining experimental data, six rabbits were anesthetized again at fixed inspiratory anesthetic concentrations. All concentrations were kept constant for 36 min and increased (or decreased). ERG waveforms were recorded every 3 min and their changes were expressed in terms of a compressed array. The array was drawn by manual shifting of the starting point diagnonally on the X–Y recorder connected to the memory oscilloscope.

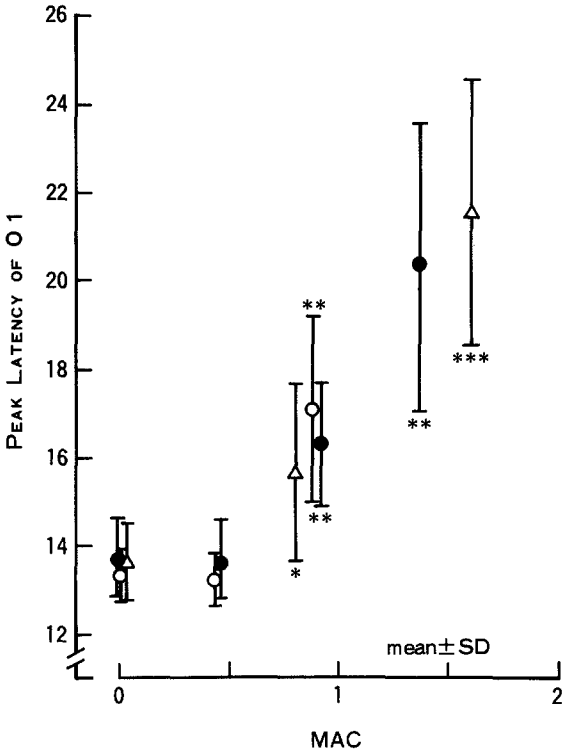

Fig. 1. The relationship between the minimum alveolar concentration (*MAC*) multiple and peak latency of the first oscillatory component (*01*). Methoxyflurane (○), halothane (△) and enflurane (●) cause a significant prolongation of 01 peak latency in excess of 0.8 MAC. Statistically significant from control (Student's *t*-test): * $P<0.05$, ** $P<0.01$, and *** $P<0.001$

Results

The effects of volatile anesthetics on the rabbits' ERG and mean arterial pressure are summarized in Table 1. The 01 peak latency was significantly increased at an anesthetic

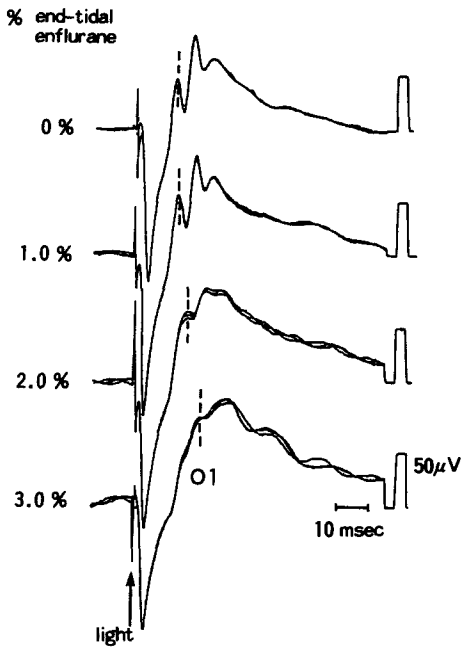

Fig. 2. Examples of ERG traces at various end-tidal concentrations of enflurane. The peaks of the first oscillatory component (01; *dotted line*) are progressively prolonged at increasing anesthetic depth. The amplitudes of the initial two or three oscillatory components are significantly reduced at increasing anesthetic concentrations in this trial

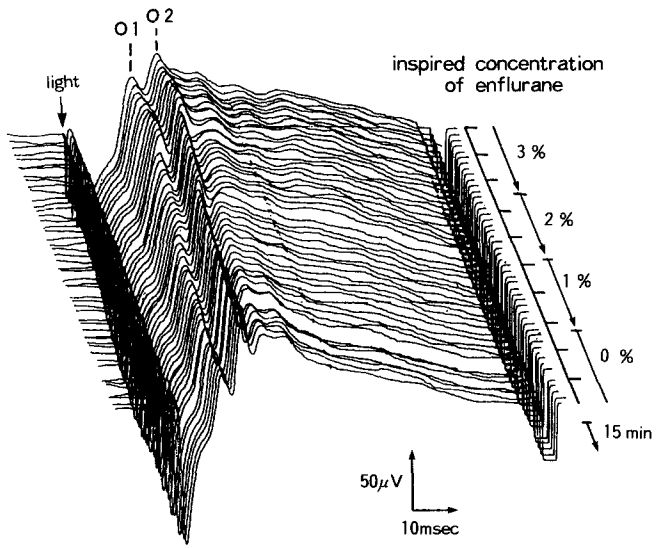

Fig. 3. The compressed array of ERGs recorded every 3 min when inspired enflurane concentrations were reduced at an interval of 36 min. The peak latencies of the first and second oscillatory components (01 and 02) were rapidly shortened after the inspired anesthetic concentration was reduced

concentration of 0.8 MAC or more. A similar dose-dependent relationship was observed between the peak latency and MAC multiples in an excess of 0.8 MAC of all anesthetics examined (Fig. 1). In sharp contrast, the peak latency of the a-wave did not change at all with any anesthetic at any concentration examined. The amplitude of both the a-wave and the 01 showed dose-related but less striking changes than did the 01 peak latency. An example of ERG traces at varying anesthetic concentrations is shown in Fig. 2. Similar changes were observed in all anesthetics examined. The coincidence of three succesive waveforms at the same concentration indicates that the ERG recording is fairly reproducible. Mean arterial pressure fell with increasing anesthetic concentration (Table 1). Arterial blood-gas analysis showed no abnormality in PaO2, PaCO2, pH, or base excess throughout the experiment.

The compressed array of serial ERG taken at 3-min intervals is shown in Fig. 3. Rapid changes in the 01 peak latency were observed immediately after the inspiratory concentrations of enflurane was reduced in a stepwise fashion from 3% toward zero.

Discussion

Our data clearly indicate that a dose-dependent prolongation of the 01 peak latency occur with anesthetic concentrations in an excess of 0.8 MAC and that this change is in common with all anesthetics examined. Surgical patients are usually anesthetized with over 1.2 MAC of inhalational anesthetics, so that the 01 peak latency will be a good indicator of the depth of inhalational anesthesia. Although both amplitudes of the a-wave and the 01 also show dose-related decreases with increasing anesthetic concentration, the changes are less marked than those of the 01 latency. The technical difficulty in estimating the amplitude is another disadvantage to the use of the 01 amplitude as an indicator of anesthetic depth. Volatile anesthetics, especially methoxyflurane, decreased mean arterial pressure to a minimum of 63 mmHg in this study. This decrease appears to have no appreciable influence on the ERG as retinal blood flow remains stable by autoregulation in the range of 55 to 225 mmHg (Demant et al. 1982).

There have been several reports about the effects of anesthetic drugs on the ERG since the classic work of Granit (1932). The results, however, are not consistent. For instance, Gerritsen (1970) reported the absence of ERG changes during halothane or ether anesthesia in rabbits while the ventilation was kept sufficient. In contrast, Raitta et al. (1979) reported that in patients under 67% nitrous oxide – 1% halothane anesthesia, the amplitudes of the a- and b-waves were diminished, whereas their latencies remained unchanged. Although we did not measure the amplitude or latency of the b-wave, changes of the a-wave were similar to those in their result. The amplitude of the a- and b-waves may be used as an indicator of anesthetic depth. However, our present data indicated that the 01 peak latency is a better index of anesthetic depth than the amplitude of the a-wave. Although interpeak latencies of the oscillatory components were not analyzed in this study, they are other index candidates of anesthetic depth.

Halothane has been reported to have a dose-related retarding effect on the time course of cone dark adaptation while exerting no influence on the waveform of the slow ERG components (Norren and Padmos 1975). Rod saturation occurred at different background levels with different anesthetics, pentobarbital, and urethane in the b-wave increment threshold study of Brown and Green (1984). These may imply that both anesthetics and anesthetic depth affect the light adaptation in the retina and cause changes in the fast ERG components. Therefore, we analyzed the ERG waveforms in the steady state, which was confirmed by their reproducibility.

There have been many reports indicating the origin of each components of the ERG. Wachtmeister and Dowling (1978) assumed that the oscillatory potentials would represent possible feedback synaptic circuits initiated by the inner nuclear layer in the retina where γ-amino-butyric acid (GABA) and glycine act as inhibitory neurotransmitters. In their study, the oscillatory potentials of the mudpuppy retina selectively disappeared when these substances were administered. Cheng and Brunner (1981a, b) found that volatile anesthetics inhibit GABA disposal and cause its accumulation at synaptic sites. In their opinion, GABA accumulation causes anesthesia. This supports the present result that the oscillatory component was most sensitive to the anesthetics.

The oscillatory components have been considered of clinical importance in patients with diabetic retinopathy, as well as other known retinal ischemic diseases. Even in prediabetic eyes with no visible abnormalities detected by ophthalmoscopic examination, the oscillatory components are delayed in peak latency with or without reductions in amplitude (Yonemura et al. 1978). Therefore, the effect of anesthetics on diabetic patients should be studied before this technique is applied in clinical settings. There are other problems to be solved before its clinical application. For instance, a long-term repeated light stimulus with high intensity may induce degenerative changes in the pigment epithelium, which probably shows the highest metabolic rate among all the cells in the body. Induced mydriasis will abolish important vital signs, such as light reflex, pupil size, and lacrimation.

Raitta et al. (1982) pointed out that the VEP was differently affected by different volatile anesthetics. Compared to the sensory-evoked cortical response, the ERG would afford advantages for the following reasons: (1) no necessity to average; (2) cheaper instrumentation; (3) larger evoked potentials that are easier to record; (4) less individual variations; (5) MAC-dependent and non-specific changes for each volatile anesthetic. The last point may ensure that it works even in the combined use of inhalational anesthetics. Moreover, anesthetic effects on the ERG appeared different from the hypoxic effect, which caused a significant prolongation of the a-wave peak latency with reduction in amplitude, followed by the changes in the oscillatory components (Tashiro et al. 1983).

In summary, the peak latency of the first oscillatory component is prolonged at clinical levels of inhalational anesthesia. The present method will be potentially useful in monitoring anesthetic levels when harmful complications due to successive ERG recordings are excluded. Furthermore, if ERG recordings during general anesthesia are necessary for ophthalmological purposes, the patient's condition must be taken into account, as it is influenced by the depth of the anesthesia.

Acknowledgements. This research was supported by Grant-in-Aid for Scientific Research C-60570720, from the Ministry of Education, Science and Culture, Japan.

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Received January 13, 1986 / Accepted April 29, 1986