Effects of Different Speeds of Induction with Sevoflurane on the EEG in Man

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The effects of two kinds of induction speed of sevoflurane anesthesia on the EEG pattern were compared in the same individual using medical student volunteers: a first exposure of 4% was given, followed after full recovery, by incremental doses of 1, 2 and 4% successively, each being administered for 10 min. The arterial blood level of the anesthetic was measured using gaschromatograph. The changes of EEG pattern during fast induction with 4% were not represented by the abbreviation of those observed during the slow induction with the incremental doses. The administration of 4% induced a sudden appearance of high voltage, rhythmic slow waves of 2–3 Hz at 1–3 min when the arterial blood anesthetic level increased maximally, which was then followed by a pattern of faster activities of 10–14 Hz mixed with 5–8 Hz slow waves. In contrast, the administration of incremental doses induced an increase in frequency and amplitude of EEG activities in the light plane, followed by their decreases in deeper planes. The final EEG patterns were identical for both these methods of induction. These findings confirmed our previous hypothesis that not only the arterial blood level of anesthetics but the rate of its increase are important factors determining the EEG pattern of anesthesia. (Key words: sevoflurane, EEG, speed of induction, high voltage rhythmic slow waves, arterial blood level)

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Fifty years have passed since Gibbs et al.[1] proposed measuring the depth of anesthesia by EEG pattern, and numerous data have been reported to confirm this rationale[2–4]. In the 1950's, Faulconer and Bickford extended this view and correlated the slowing of EEG activities with an increase in the arterial blood level of ether[5]. Comparing various types of EEG slow waves observed during anesthesia and surgery, we reported that the arterial blood level of anesthetics, though decisive, was not the final determinant of their EEG patterns[6]. Additional factors such as the speed of administration[6,7], the duration of administration[8,9], application of noxious stimulation[10,11], and the age of patients[12], all may significantly alter the EEG pattern. With regard to the effects of different speed of administration, we reported that fast induction with halothane or thiamylal induced peculiar EEG patterns which were different from those observed during slow induction or a steady state. The blood/gas partition coefficient of the recently developed new anesthetic, sevoflurane, is extremely small, i.e., 0.59[13], and

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Table 1. Arterial blood level of sevoflurane in five volunteers (mg %)

No. of subj.	Inspired concentration and time (min)					
	2	4 % 4 – 5	10	1% 10	2% 10	4% 10
1	–	12.414	13.060	3.777	7.330	–
2	6.125	13.750	14.403	2.845	8.068	13.656
3	–	12.843	13.317	4.098	7.780	10.316
4	13.253	13.713	14.274	3.864	7.312	12.685
5	11.904	–	13.693	3.600	7.669	12.413
mean	10.6	13.2	13.7	3.6	7.6	12.3
SD	3.9	0.6	0.6	0.5	0.3	1.4

the rate of rise in the alveolar concentration is extremely rapid. There is a possibility that the EEG pattern differs between the induction phase and the period of maintenance even when the arterial blood levels of the anesthetic do not differ significantly. It is our attempt to examine our hypothesis that the rate of rise in the arterial blood level of anesthetics influences the EEG pattern.

Methods

Five male medical student volunteers, in weight 60–72 kg, and in age 23–25 years, were the subjects in this study. Informed consent was obtained before the study. All subjects were in normal physical status. No preanesthetic medication was given. Prior to the induction of anesthesia, indwelling catheters were inserted, under lidocaine local anesthesia, in the radial artery for direct measurement of arterial blood pressure and collecting blood samples, and in the cephalic vein for fluid infusion. Disc electrodes, filled with electric paste, were placed at the bilateral frontal, parietal and occipital areas, with the reference being placed at the bilateral ear lobes. The EEG activities were recorded on a 10 channel recorder (Sanei 1A91) and on a magnetic tape simultaneously (TEAK MR30). The frequency power spectrum was obtained using a signal processor (Sanei 7T18) offline from the magnetic tape. The arterial blood level of sevoflurane was measured by a gas chromatograph (Shimadzu GC6AM), using the whole blood injection technique and flame ionization detector at a temperature of 100°C.

All subjects were exposed to sevoflurane twice. Initially 4% sevoflurane in oxygen was given for 10 min, after which the anesthetic was discontinued and full consciousness was regained. Approximately 60 min later, three incremental concentrations of 1, 2 and 4% in oxygen, were given successively, each step being maintained for 10 min. The respiration was left uncontrolled initially, then assisted or controlled manually as required. The end-expiratory CO_2 level was monitored continuously using an infra-red analyzer (Nihonkoden OIR-7101), and confirmed by serial arterial blood samples (Radiometer ABL 2). The arterial blood sampling for measuring blood level of anesthetic was done at 2, 4 or 5 and 10 min during fast induction, and at 10 min of each step during slow induction.

Results

The changes in the arterial blood level of sevoflurane are summarized in table 1, and their graphic presentation is shown in fig. 1. During induction with 4% sevoflurane, the arterial blood level increased rapidly to reach 10.6 ± 3.9 mg % at 2 min, and 13.2 ± 0.6 mg % at 4–5 min, after which a slight increase was attained. During slow induction with the incremental concentrations, the arterial blood level showed a gradual increase to reach 12.3 ± 1.4 mg % at the end of 4% administration. The changes in the arterial blood pressure and heart rate are summarized in table 2. The circulatory system was not markedly depressed by either methods of induction.

Administration of sevoflurane, 4% in oxygen, induced loss of consciousness within 2 min, which coincided with the sudden appearance of high amplitude (100-200 μv), rhythmic slow

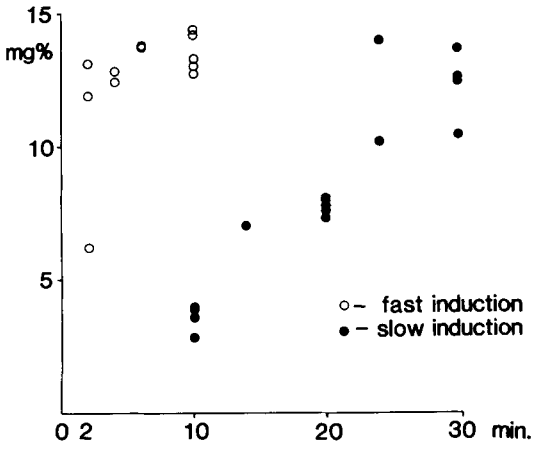

Fig. 1. Changes of arterial blood level of sevoflurane. Open circles indicate the concentrations of sevoflurane, in mg %, during fast induction with 4 %, and the filled circles those during administration of incremental doses. Note that, during fast induction, it reached almost 80 % of the final concentration at 2 min.

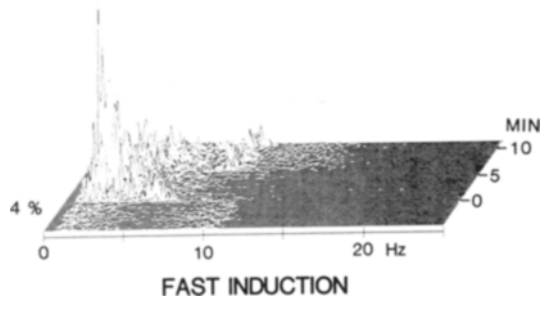

Fig. 3. Power spectrum array of EEG during fast induction with 4 %. The original EEG is partly shown in fig. 2. Abscissa indicates frequency and the ordinate the power. Each line represents the average of 4 records of 16 sec duration. Note the sudden increase in the power of 2–3 Hz activities at 2 min. There are two peaks of power at 2–6 Hz and 10 Hz at 5 min.

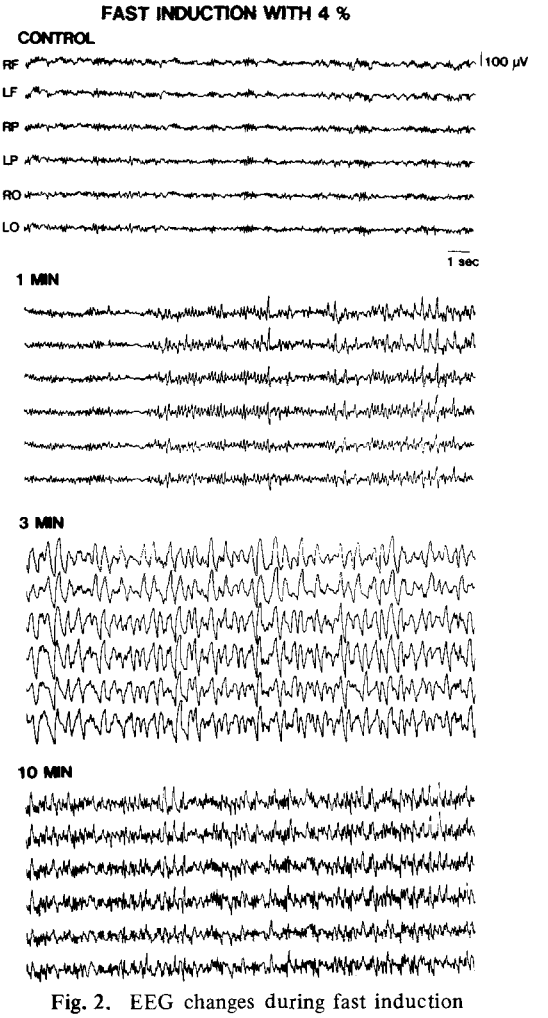

Fig. 2. EEG changes during fast induction with 4 % sevoflurane in a 24 year old male volunteer. RF: right frontal; RP: right parietal; RO: right occipital; LF: left frontal; LP: left parietal; LO: left occipital. The reference electrodes were placed at the ipsilateral ear lobe. The amplitude increased and the frequency decreased at 1 min. The typical high amplitude, rhythmic slow waves appeared at 3 min. The rhythmic slow waves disappeared and 10–14 activities appeared at 10 min. Apparently the EEG activities are faster at 10 min than at 3 min.

Table 2. Changes in the circulatory system

No. of subj.		control	fast induct. 4 % 5 min.	fast induct. 4 % 10 min.	control	slow induction 1 % 10 min.	slow induction 2 % 10 min.	slow induction 4 % 10 min.
1	S	127	119	117	142	120	113	112
	D	70	70	66	77	66	62	56
	HR	59	68	59	58	52	51	54
2	S	130	115	110	135	127	108	105
	D	75	67	60	77	70	66	60
	HR	68	60	62	70	65	67	64
3	S	137	126	114	138	118	120	110
	D	77	70	62	80	75	60	60
	HR	79	77	71	77	75	77	68
4	S	135	98	100	138	118	98	98
	D	70	50	55	78	62	58	54
	HR	70	44	56	64	52	62	54
5	S	136	134	103	136	127	108	101
	D	70	69	62	74	69	65	61
	HR	60	64	81	79	65	70	73
mean Syst		133.0	118.4	108.8	137.8	122.0	109.4	105.2
SD		4.3	13.5	7.2	2.7	4.6	8.1	5.9
mean Diast		72.4	65.2	61.0	77.2	68.4	62.2	58.2
SD		3.4	8.6	4.0	2.2	4.8	3.4	3.0
mean HR		63.2	62.6	65.8	69.6	61.8	65.4	62.6
SD		5.4	12.2	10.2	8.8	9.8	9.7	8.5

S: systolic pressure in mmHg; D: diastolic pressure;
HR: heart rate; SD: standard deviation.

waves (2–3 Hz) (1 and 3 min in fig. 2, fig. 3, and left column of fig. 4). This EEG pattern was dominant for 2–3 min, and was then replaced gradually, toward the end of the test period, by a pattern of faster activities of 10–14 Hz, 50–100 μv, mixed with 5–8 Hz, 50–100 μv activities (10 min in fig. 2, and fig. 3 and 4).

Administration of incremental doses of sevoflurane, 1, 2 and 4%, induced a gradual change in the EEG from the control pattern to that of greater amplitude and slower activities (right column of fig. 4, and fig. 5 and 6). Sevoflurane, 1% in oxygen, did not induce significant change in the EEG and the subject did not become unconscious. At a 2% inspired concentration the amplitude of EEG activities remained relatively unchanged, but the frequency increased to 10–14 Hz and induced unconsciousness in all subjects (fig. 5). At 4% inspired concentration, the amplitude still increased to 100–200 μv, and some slower activities of 5–8 Hz, 50–100 μv appeared. This final pattern was identical, by both visual inspection and on the power spectrum frequency array, to the final pattern induced by the rapid induction with 4% (fig. 2–6).

Discussion

The present study showed that the difference in the rate of increase in the arterial blood level of sevoflurane induced a distinguishable difference in the EEG pattern, and confirmed our hypothesis derived from studies using halo-

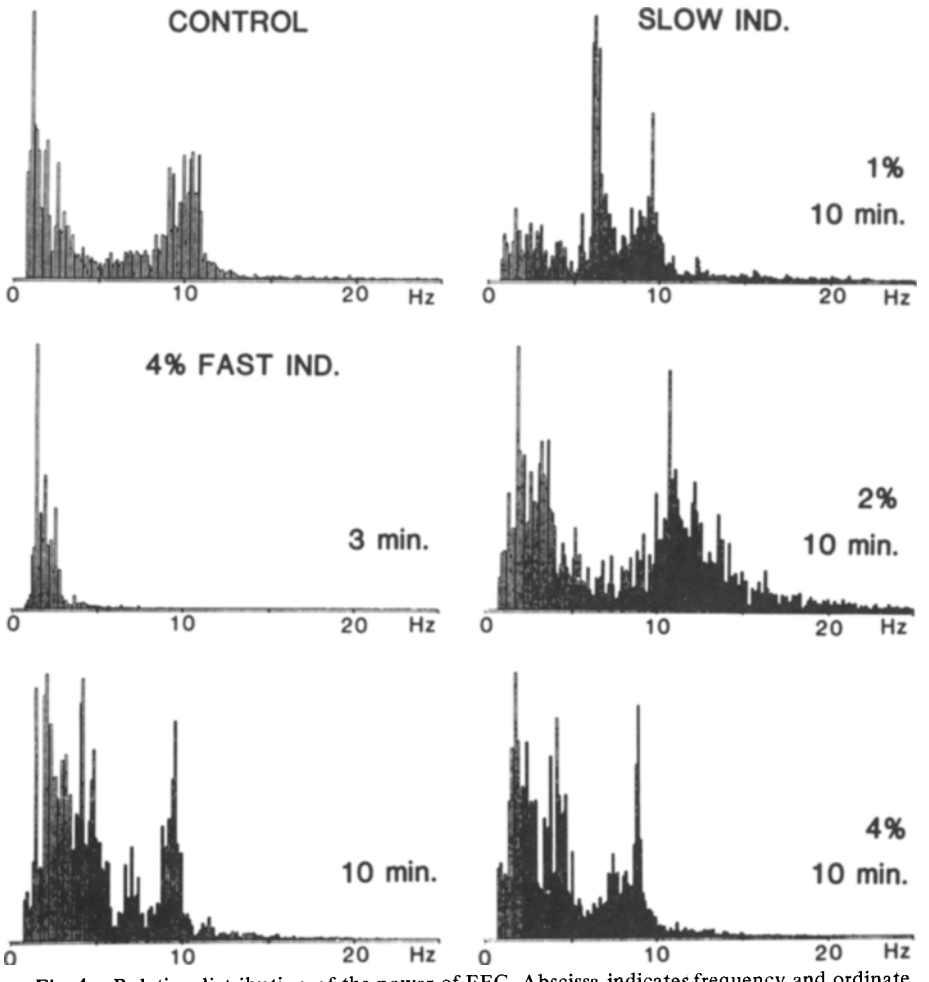

Fig. 4. Relative distribution of the power of EEG. Abscissa indicates frequency and ordinate the power distribution. The left three figures show the control, and those during fast induction, and the right three figures show those of 1, 2 and 4 % incremental doses. Note the peculiar distribution at 3 min of fast induction: there is a peak in 2–4Hz at 3 min. The pattern of distribution at the final stage of both induction methods is similar.

thane and thiamylal. During fast induction, when the arterial blood level increased at the maximum rate at 1–3 min, a peculiar pattern of high voltage, rhythmic slow waves appeared, which was not observed during the whole course of slow induction. Although the EEG patterns during induction were different for these two methods of administration, their final EEG patterns were identical as determined by visual inspection and power spectrum analysis. There is a possibility that in so far as the rate of increase in the arterial blood level is limited to a certain range, an EEG pattern similar to that recorded during the steady state of anesthesia appears even during induction phase. Above this range, however, the fast induction type EEG appears. The present study, however, was not designed to detect the exact range of this rate of increase. Another interesting finding was that the slow wave EEG, appearing at 1–3 min, was replaced by a fast wave EEG toward the end of administration of 4% sevoflurane. This occurred when the arterial blood sevoflurane level was still increasing though the rate of increase had already become small. These findings are opposite to the traditional view that the greater the arterial blood level of anesthetics, the slower the EEG activities, and indicate that when the

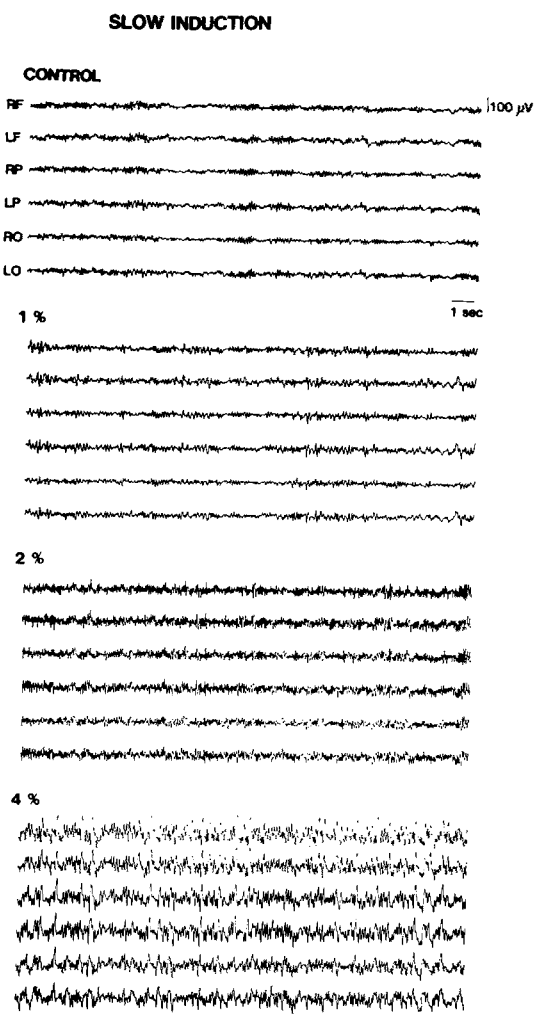

Fig. 5. EEG changes during slow induction with incremental doses of sevoflurane, 1, 2 and 4%, in the same individual as in fig. 2. The abbreviations are the same as those in fig. 2. Each record was obtained at the end of 10 min administration of each concentration. The record at 4 % seems identical to the final record of fast induction in fig. 2.

rate of increase exceeds a certain range, the traditional view does not hold valid.

The high voltage, rhythmic slow wave pattern, which appeared during fast induction, is not specific to the drug. Similar EEG patterns appear in several situations during anesthesia. Firstly, cyclopropane, ether and ketamine, which activate the reticular neurons, all induce this EEG pattern in human and laboratory animals[6,8,14–16]. Nitrous oxide, which also

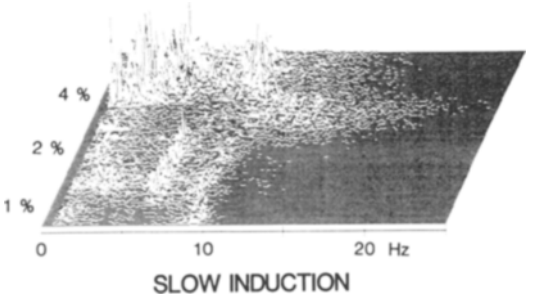

Fig. 6. Power spectrum array of EEG during slow induction. The original EEG is partly shown in fig. 4. The abbreviations and the method of illustration are the same as those in figure 3. Note the small peak at 12–16 Hz at light anesthesia with 2%, which is absent in fig. 3.

activates the reticular neurons, induces this EEG pattern when it is added to halothane or methoxyflurane in humans[9,17]. Secondly, this EEG pattern appears in human infants and children when noxious stimulation is given under halothane-oxygen anesthesia[10,11]. Thirdly, it appears in cats when high frequency electrical stimulation is given to either the skin or the brain stem reticular core during anesthesia with various agents[6,18–20]. All these indicate that the EEG pattern of high voltage rhythmic slow waves is a sign of CNS stimulation during anesthesia as was discussed by us previously[8,10,11,16]. Although the smell of 4% sevoflurane is more intense than that of 1–2%, it is rather mild in comparison to that of halothane or methoxyflurane, and it seems that the intensity of smell is not sufficient to induce such CNS stimulation. Further, thiamylal which does not smell, also induces this EEG pattern during rapid infusion[6].

We reported previously that lidocaine produced different CNS actions when the infusion rate was different: slow infusion with 1 mg/kg/min induced tetraphasic actions such as depression, followed by activation and depression and finally generalized convulsions, while a higher rate of infusion reduced the components of CNS depression, and it induced only CNS activation when given at a rate of 15 mg/kg/min or greater[21]. These indicate the possibility that there is a general rule that CNS drug actions are determined not only by the drug content of the brain but also by the rate of its change. The

mechanisms by which different rates of increase in the brain content of drugs induces different CNS actions remains obscure.

The MAC of sevoflurane is 1.7 %[22], and the inspired concentration of 4 %, used in the quick induction case in the present study, is only 2.4 times MAC. A higher concentration than this should be used in daily practice with sevoflurane anesthesia, and the effects of speed of induction of anesthesia on the CNS functions are something more than a scientific interest.

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