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Adequate hypnosis at very low isoflurane concentration during craniotomy monitored by electroencephalography

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Abstract
We report a patient with Parkinson's disease undergoing craniotomy for a brain tumor, who had clinically adequate hypnosis at a very low concentration of isoflurane. While the raw EEG showed low-voltage slow electrical activity, the EEG analyzer of the monitor displayed high burst suppression ratios. The role of intracranial pathology and drug therapy as possible causes of the low anesthetic requirement for adequate hypnosis are discussed. This report also draws attention to the possibility of erroneous analysis of burst suppression by EEG modules.

Key words Burst suppression · EEG · Isoflurane · Anesthesia · Brain tumor · Parkinson's disease

Introduction

Central nervous system pathology and drugs used in the treatment of central nervous system disorders may have a profound influence on electroencephalographic activity, which may confound the monitoring of raw or processed EEGs. We report a case where a patient with Parkinson's disease undergoing a craniotomy for brain tumor had clinically adequate hypnosis at a very low concentration of isoflurane. While the raw EEG showed low-voltage slow electrical activity, EEG-derived parameters did not indicate the depth of anesthesia correctly.

Case report

A 40-year old woman presented with a history of headache associated with nausea and vomiting for 6 months. On examination she was conscious, and oriented to time, person, and place. Results of systemic examination were within normal limits. Results of all the routine biochemical and hematological investigations were within normal limits. A lateral X-ray of the skull showed a "beaten-silver" appearance. Magnetic resonance imaging of the head showed a large left pterional meningioma with a midline shift of 5 mm.

The patient also complained of tremors in the upper extremities that had been present for 6 months. A neurological consultation led to a concurrent diagnosis of Parkinson's disease on the basis of pill-rolling tremor, rigidity, and bradykinesia. She was treated, over a period of 15 days, with escalating doses of Syndopa (M/S Sun Pharmaceutical Industries, Mumbai, India) tablets, each tablet containing 100 mg levodopa and 10 mg carbidopa. The initial dose was half a tablet twice a day and the final maintenance dose just before surgery was one tablet four times a day (400 mg levodopa and 40 mg carbidopa per day in four divided doses). Her tremor was also treated with clonazepam 0.5 mg daily for 6 days before surgery.

In the operating room, anesthesia was induced with fentanyl 125 μg and thiopentone 300 mg. Tracheal intubation was facilitated by vecuronium bromide 8 mg and lignocaine 100 mg. Anesthesia was maintained with air-oxygen-isoflurane and intermittent boluses of fentanyl and vecuronium. Intraoperative monitoring consisted of electrocardiogram, invasive blood pressure, capnography, and pulse oximetry. Following the induction of anesthesia and surgical positioning, bipolar scalp cup electrodes (Fp_2-T_4 and C_4-O_2) were placed for monitoring two EEG channels on the side contralateral to the tumor (Fig. 1). As soon as the electrodes were placed, both the EEG channels displayed low-voltage slow waves. Despite the fact that there were no bursts or suppression of the EEG, the monitor displayed burst suppression ratios (BSRs) of 90% and 60%, respectively, in the Fp_2-T_4 and C_4-O_2 channels. At this point of time, the endtidal isoflurane concentration (ET_{iso})

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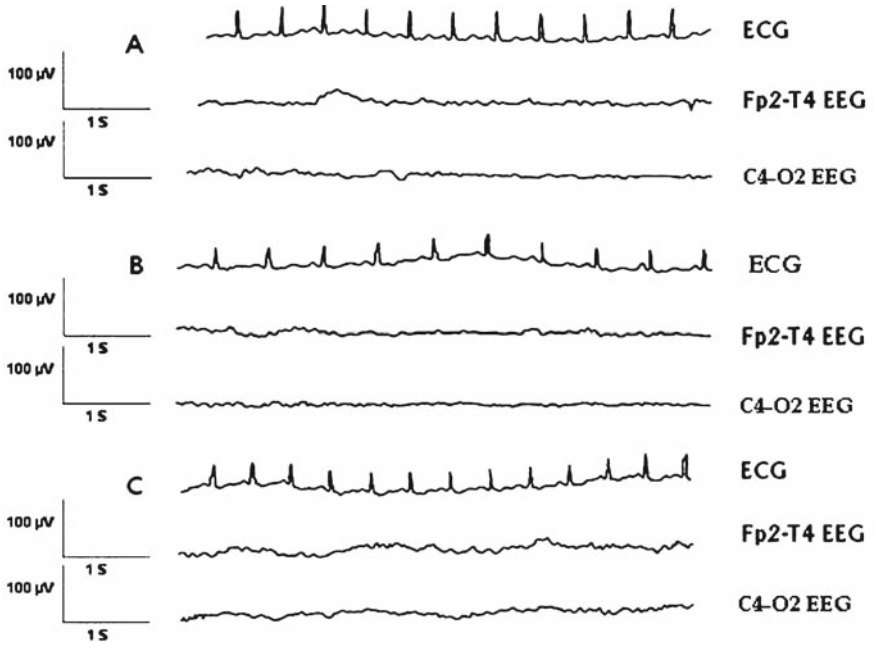

Fig. 1. Intraoperative recordings of two channels of EEG and ECG. *A* At 30 min after induction of anesthesia; *B* at 180 min after induction of anesthesia; *C* at end of surgery

Table 1. EEG parameters displayed by the monitor at 30 min and 180 min after induction

	Fp_2-T_4			C_4-O_2		
	At 30 min	At 180 min	End of Surgery	At 30 min	At 180 min	End of Surgery
SEF	8.6	5.5	5.1	9.8	3.1	4.3
Amplitude (µV)	6.5	10.6	17.2	3.2	7.6	7.3
Delta %	94	92	93	96	98	94
Theta %	5	7	4	4	2	3
Alfa %	5	1	1	1	1	2
Beta %	1	0	1	0	0	0
BSR	86	65	10	85	93	78

SEF, spectral edge frequency; BSR, burst suppression ratio

was 0.5 % and the vital parameters were as follows: heart rate (HR), 71 beats per min (bpm); blood pressure (BP), 111/74 mmHg; and endtidal CO_2 pressure (Pet_{CO_2}), 31 mmHg. The low-voltage slow electrical activity without any evidence of burst suppression persisted despite decreasing the ET_{iso} to 0.2%–0.4%, while the monitor still continued to show very high burst suppression. The EEG variables as displayed by the monitor at 30 min and 3 h after the induction of anesthesia are shown in Table 1. The vital parameters at 3 h were: HR, 103 bpm; BP, 134/74 mmHg; Pet_{CO_2}, 29 mmHg; and ET_{iso}, 0.2%. After discontinuation of the anesthetic at the end of surgery, the amplitude and the frequency of the EEG recovered significantly faster in the FP_2-T_4 channel than in the C_4-O_2 channel. The neuromuscular block was antagonized with atropine and neostigmine and the trachea was extubated 15 min later. The patient was drowsy but obeying commands. She did not have any recall of the intraoperative events despite the very low concentration of isoflurane used during the surgery. A 16-channel EEG recorded on postoperative day 7 showed no abnormality.

Discussion

The interesting feature of this case report is the clinically adequate anesthesia achieved at a very low isoflurane concentration. The raw EEG showed low-frequency low-amplitude activity at an endtidal isoflurane concentration of 0.2%–0.4%. The monitor spuriously displayed a high degree of burst suppression at this concentration; this contrasts with the concentration of isoflurane required to produce burst suppression

in various earlier studies, which varied between 1.25% and 1.7% [1–3].

Previous reports have shown that EEG monitors, including bispectral index monitors, may display spuriously high BSR values without evidence of bursts on the raw EEG [4,5]. This fallacy results from misinterpretation of the low-amplitude EEG as burst suppression by the monitor. This could have been the case in our patient, resulting in a mistaken judgment that the patient was under deep anesthesia, while the raw EEG did not suggest such a profound depth of anesthesia. It was, in fact, difficult to assess the level of hypnosis from the EEG pattern. However, the facts that the patient required 15 min to become fully awake after isoflurane was discontinued and that she did not have any intraoperative recall confirm that the depth of anesthesia was adequate even at such a low anesthetic concentration. Subjecting the EEG to analysis by another EEG analyzer would have correctly quantified the amplitude and frequency of the raw EEG. Such an exercise could not be undertaken, as the EEG was not recorded in a format that was amenable to subsequent offline analysis.

The probable causes of the low-voltage and low-frequency EEG and the satisfactory clinical anesthesia at a very low isoflurane concentration, 0.2 minimum alveolar concentration (MAC), are not clear. These findings could have been a result of the patient's intracranial pathology or her preoperative medications. The patient might have had such an EEG abnormality preoperatively, which disappeared with the excision of the tumor. Alternatively, her preoperative EEG could have been normal and the low-voltage slow EEG observed during surgery at a very low isoflurane concentration could have been the result of some intraoperative factors. Frequency and amplitude EEG changes that are proportional to the level of consciousness are reported in patients with rapidly growing tumors, but not in those with slowly expanding noninfiltrating lesions [6], such as that seen in our patient. Our patient was conscious and had a slow-growing meningioma. Low-voltage EEG, which is reported in about 4% of the normal population [7] can be ruled out as a cause of the EEG changes seen in our patient, by the normal postoperative EEG. Cerebral ischemia as a cause of the low-voltage and low-frequency EEG in our patient was excluded by the absence of causative factors such as significant brain retraction, hypotension, hypovolemia, hemodiution, and severe hypocapnia or hypoxia in the intropeative period. The uneventful recovery of our patient, without any neurological manifestations, also excludes intraoperative cerebral ischemia.

Levodopa causes a slight increase in basic background frequency [8] or a localized increase in the power in all EEG frequency bands [9]. Our patient, though on levodopa, had a significant decrease in EEG activity even at a very low anesthetic concentration. Clonazepam alone is unlikely to have been the cause of the low EEG frequency and amplitude, as the dose received by the patient was very small.

It appears that, in our patient, several factors—intracranial pathology, benzodiazepine use, and isoflurane—together were responsible for the low-voltage, low-frequency EEG and clinically satisfactory anesthesia at a very low anesthetic concentration. Of these factors, we propose a mechanism of clonazepam-isoflurane interaction. While clonazepam acts at the interface between the α and γ subunits of γ-aminobutyric acid $(GABA)_A$ receptors, isoflurane acts at the TM_1, TM_2, and TM_3 domains of the transmembrane regions of the same $GABA_A$ receptors [10]. Because both agents act at different parts of the same receptor, there could have been a synergistic interaction between the two, resulting in adequate hypnosis even at a low isoflurane concentration.

The faster recovery of EEG activity in the Fp_2-T_4 compared to the C_4-O_2 channel after discontinuation of anesthesia in our patient may be explained on the basis of the differential effects of anesthetics on the EEG activity of various areas of the brain. Studies have shown that the topographic distribution of intraoperative EEG responses is not homogeneous during isoflurane anesthesia [11]. These spatial inhomogeneities have been reported to have a frontal dominance [12] and to vary with the depth of anesthesia [13,14]. In the present patient, at the time of extubation, the EEG was probably in the process of returning to baseline, with Fp_2-T_4 EEG showing a more rapid reversal of the amplitude and frequency than the C_4-O_2 EEG channel.

To conclude, we could adequately manage our patient at a very low concentration of isoflurane by monitoring the EEG waveform, although the parameters as calculated by the EEG monitors did not correctly indicate the depth of anesthesia.

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