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EEG-Derived Indexes for Deep of Anesthesia and Hypnotics

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Abstract: ***Recently deep of anesthesia monitoring is always a part of multimodal anesthesia monitoring. Most popular are EEG-based indexes as BIS, evoked potentials and entropy. Anaesthetics have variable influence on the EEG-derived indexes. The aim of this review is to show the effect of the mostly used hypnotics on the EEG-derived indexes.***

Keywords: deep of anesthesia, EEG-derived indexes, hypnotics, muscle relaxants

1. Introduction

The most common use of the hypnotics is in the introduction to anesthesiaas a single bolus dose. Anesthesiadeepens rapidlydue to itsleading to a loss of consciousness, it reaches the highest point andthen it decreases along withthe decreasein plasma concentrationas the drug distributes rapidly.

Central nervous system (CNS)suppression is a function of the plasma concentration of hypnotics and it can be presented graphically as a hysteresis curve.

The clinical symptoms indicative for the depth of anesthesia at the time of its introduction include: a loss of verbal response, an absent blink reflex, an absence of body movement when squeezing of the trapezius muscle is performed. The hypnotics do not provide enough analgesia.That is why the hemodynamic response to unpleasant pain stimulation is significant, even with high doses applied. Consequently, when monitoring the anesthesia depthby clinical symptomsat the time of severe painful stimulation (laryngoscopy, intubation), a concomitant administration of analgesics and adjuvant drugs (opioids, laughing gas, muscle relaxants) is required to provide a hemodynamic stability.

Since the early 1990s, mathematical and statistical analyses of EEG have been carried out, making it possible different monitors to be introduced in the clinical practice forestimation of the depth of anesthesia. Such monitoring is not an evolution, but rather a revolution in the conducting anesthesia. The greatest experience in the practice and the most large-scale researchespublished concern BIS-monitor for the depthof anesthesia.Second place takes EEG-derived index entropy (10,13,15) and aural evoked potentials.

Maintaining of anesthesiaby intravenous hypnotics becomes preferable way with the introduction of Propofol into practice. But no equivalent exists to the end-tidal concentration of inhaled anaesthetics. In computer-controlled target infusions for Propofol, a pharmacokinetic model calculates the required plasma concentrations. This model, however, does not always coincide with the actual values because of the significant individual differences in the pharmacokinetics. In addition, there are differences in the clinical effect of the drug to the individual patients (14). These peculiarities make it difficult to determine the depth of anesthesiaas well as the prevention of staying awake, especially in case of concomitantadministration of muscle relaxants.

Sear J. W. et al. (16) suggest a Minimum Infusion Speed (MIS) concept so that the required doses of intravenous anaesthetic during TIVA (Total intravenous anesthesia)to be compared. They calculate 50% effective dose (ED50) and a 95% effective dose (ED95) according to the presence of motor response to the skin incision, similarly to MAC (the Minimum Alveolar Concentration) of inhaled anaesthetics. Unfortunately, so defined Minimum Infusion Speed (MIS) is influenced also by the pharmacokinetic properties of the drug, by the age and physical status of the patient and the concomitant use of other drugs (opioids, laughing gas), as well as bythe central nervous system reactivity and its response to the anaesthetics (11). In the clinical practice, intravenous hypnotics are often combined with other drugs (opioids, laughing gas and potentinhaled anaesthetics) in order to suppress the hemodynamic response to strong clinical stimuli such as laryngoscopy and intubation.

Kazana T. et al. (7) have found out that an equivalent plasma concentration of Fentanyl of 3 ng/ml reduces Cp50 values of Propofol by 50-55% when applying intensive pain stimuli.

The influence of hypnotics on EEG changes is a subject of a large number of studies. According to the most of the researchers, the response to EEG signal depends on a series of factors (4, 6, 12, 14).

The study conducted by Iselin-Chaves I. A. et al. (4) concerning BIS when introducing inanesthesiawith Propofol is intended to establish:

- What is the foreseen concentration of Propofol at which concentration the patient loses their consciousness (they do not respond to verbal stimuli)?
- What is the value of BIS corresponding to this concentration?
- What is the foreseen concentration at whichconcentration BIS value becomes 60?

According to the authors of the study, such information would help to individualize the dose of Propofolfor achieving a loss of consciousness. They found out that

addition of morphine reduces the concentration required for Propofol but it has a slight effect on BIS values.

Similar results are obtained byKatoh T. et al. for the inhaled anaesthetic Sevoflurane (5, 6) too. The results are indicative that Fentanyl in a standard dose reduces the required hypnotic concentration by about 60%, but at the time ofawaking, the decrease is not more than 24%. These results indicate that the calibration of the concentration of hypnotics needed to achieve a loss of consciousness is slightly influenced by the presence of morphine. In order to be reduced the frequency of preoperative memorization, it is desirable when maintaining anesthesianot to reduce the foreseenconcentrations on the spot below the values required for loss of consciousness.Such a foreseen concentration may vary by 20-30%, depending on the presence or absence of morphine and premedication. The indicated titration algorithm is not applicable if morphine and hypnotic drugs are administered as intermittent boluses.

Spontaneous EEG changes depending on the administration of hypnotic agents are presented in Figure 1.

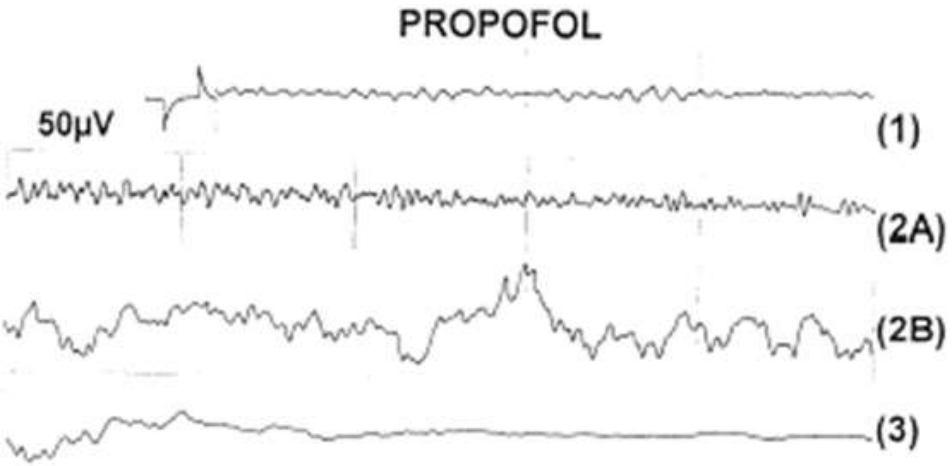

Figure 1: Change of spontaneous EEG:1 - awake,2A - activation phase,2B - predominantly slow waves,3 - "burst" suppression

Most of the monitors for depth of anesthesiabased on the cortical EEG analysis are similar. They use different algorithms to transform the complex signal (EEG) into a descriptive digital value (practically it is double with the entropy monitor), which theoretically corresponds linearly to:

- Theproportion presumable/actual concentration of the most hypnotics, excludingXenon, Ketamine and Laughing gas (11).
- The clinical sedation score.

The main problem with these monitors is that the proportion between the foreseen concentration of hypnotics and the digital value of the monitor is not strictly linear and monotone for the entire concentration range of hypnotics applied in the practice. Inconsequence of this absence of linearity comes the fact that algorithms for hypnotic titration are hard to apply. The nonlinear curve “the highest - the lowest concentration” is of differentmagnitude, depending on the specific algorithm for calculation of different monitors. Finally, the diagnostic monitoring (the distinction between the presence/loss of consciousness) may differ at low concentrations (the beginning of introduction inanesthesia or awakening), medium concentrations (maintaining of anesthesia) and high concentrations (overdose of anesthetics).

The principles of hypnotic titration over the information displayed on the different anesthesia depth monitors are not yet definedprecisely. Rather, it is considered that "hypnotics are titrated to maintain values of different indexes of EEG analysis between two definitefigures" (1, 2). Whether or not the hypnotics are administered as a continuous perfusion, intermittent bolus doses or through inhalation, index values allow the individual differences to be integrated (irrespective of the fact that they are either pharmacodynamic or pharmacokinetic).

Lambert P. et al. (8) have found out that with adult patients, the time for BIS values to reduce to 60 is 5-10 minutes, with individual variations in a given group of patients.

Ketamine

Ketamine is a well-known drug in anesthesia tools. It is used in the modern practice to improve the postoperative analgesia by preventing the acute tolerance to opioids and to reducethe postoperative hyperalgesia in patients after surgery. At the time of its administration during Propofol infusion, an increase in entropy values could be observed despite of the deepening of hypnosis.

The hypnotic effect of Ketamine is characterized by a dissociative mechanism and it has been established that the drug increases the delta activity of the EEG (3). The response of BIS to Ketamine is paradoxical, taking into consideration that anesthesiadeepenswhen adding an additional anaesthetic agent.

According to Sleigh J. W. et al. it should be considered that BIS reflects the cortical activity and not thelevel of consciousness(17). When administering Ketamine to patients anaesthetized with GABA-ergic drugs which suppressthe cortical activity such as Propofol and Sevoflurane, higher frequenciesand desynchronization were observed. Such a modification results in changes in BIS values which are not related to the depth of anesthesia. The

observed effect most probablyis due to the modification of the correlation EEG-parameters and hypnotic component of anesthesia. Ignoring such an effect can lead to unnecessary deepening of anesthesia and overdosing of hypnotic agents. Larger-scale studies are necessary which to determine whether the effect of Ketamine on EEG-entropy is dose-dependent and whether it is observed to the same extent in the presence of a varying balance between hypnosis, analgesia and surgical stimulation.

Recently Ketamine is recommended in minimal doses as a prevention drug for the postoperative hyperalgesia and opioid tolerance (9). Noone clinician should forget the known paradoxical effect of Ketamine on BIS values.

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