High estradiol levels and depth of anaesthesia

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Summary

Estradiol is a steroid-structured hormone that has a periodic rhythm in the menstrual cycle. We aimed to evaluate the interference of high estradiol levels and the depth of anaesthesia.

The study was performed on 44 females undergoing gynaelocologic surgery. Blood samples were performed for estradiol level before the procedures. BIS scores were recorded at 5-min intervals after induction and during the operation. Cases were assigned to three groups: Group 1 (n: 17) estradiol levels at or under 100 μg/dl, Group 2 (n: 14) levels were between 100 and 200 μg/dl and Group 3 (n: 13) levels were above 200 μg/dl.

Estradiol levels were found to be 59.94 ± 23.59 μg/dl in Group 1, 138.60 ± 23.49 μg/dl in Group 2 and 239.30 ± 41.08 μg/dl in Group 3. Significant differences were found between initial control and 10 and 80 min BIS levels.

Anaesthetic consumption showed a decreased tendency in high estradiol cases. We concluded that an advanced clinical series should be performed to fully define the relationship between estradiol levels and anaesthesia depth.

Key words: Anaesthesia; Estradiol; Depth; BIS.

Introduction

General anaesthesia is characterized by loss of consciousness, amnesia, and immobility in response to noxious stimuli. This includes not only analgesia and hypnosis, but also the suppression of somatic and autonomic responses to noxious stimuli [1]. There are so many different factors that affect depth of anaesthesia. Combined administration of anaesthetics can cause synergystic effects in practice. The quality control of anaesthesia has become increasingly important, owing to the recent evolution in perioperative management. Due to new surgical techniques and changing needs in patient care, it is more and more essential to find methods to manage anaesthesia in a fast, simple way, and with limited side-effects. To achieve these goals a wide spectrum of pharmacological actions need to be utilised.

The Bispectral Index® (BIS®) is a measure of the effects of anaesthesia and sedation on the brain, a new "vital sign" that allows clinicians to deliver anaesthesia with more precision and to assess and respond more appropriately to a patient's changing condition during surgery. The potential usefulness of BIS monitoring as an indicator of the depth of hypnosis during inhalation of anaesthesia has been described [2, 3]. Unfortunately the depth of the anaesthesia has not been evaluated during the procedure in every case because of the cost of the BIS monitor. Anaesthesia levels should not be too light or too deep. Deep anaesthesia may cause a coma and finally death by depressing vital functions. On the other hand, light anaesthesia can not prevent neuroendocrine and reflex responses to painful impulses [4].

Corticosteroids may cause an anaesthetic effect when their own anaesthetic property is taken into consideration. Anaesthetic steroids have been known for years. Selye [5] showed almost 66 years ago that steroid hormones given parenterally and orally could bring about sedation and anaesthesia. Furthermore, he was able to show that it was possible to produce steroid molecules that were anaesthetics but devoid of hormonal action. Steroids are also used as analgesics [6]. It is almost impossible to measure the probable anaesthetic activity of other steroids at present. However it may be possible by evaluating interactions with anaesthetics.

Estradiol is a steroid-structured hormone that has a periodic rhythm in the menstrual cycle. Some women may have very high estradiol levels. In light of this knowledge, deeper anaesthesia may be performed in patients with high estradiol levels using lower doses of agents. To our knowledge there is no literature about the anaesthetic effectiveness of estrogen. In this study we aimed to evaluate the interference of high estradiol levels and the depth of anaesthesia. Since there may be high levels in some cases, we aimed to research estrogen as an endogen hormone, and general anaesthetic agent interaction via the BIS® monitoring.

Materials and Methods

After approval of the ethical committee, the study was performed on 44 females undergoing gynaecologic surgery. Women in the menopausal period, pregnant women, epileptic seizure cases, hormone administered cases, oral contraceptive and antipsychotic drug users were excluded from the study. Cases with operation time over 80 minutes were also excluded. All of the patients were premedicated with 10 mg diazepam and 0.5 mg atropine 30-45 minutes before surgery. After receiving blood samples to calculate estradiol base levels, intravenous

Revised manuscript accepted for publication June 16, 2005

0.9% NaCl infusion was started. Heart rate, peripheral oxygen saturation (SpO_2) and oscillometric non invasive blood pressure were monitored by an Artema Diascope Traveller 4041 monitor and control levels were recorded. Haemodynamic parameters were measured at 10-min intervals throughout the procedure. The frontal scalp was cleaned with alcohol and BIS electrodes were applied. Age, weight and operation duration variables were recorded for every case. In all patients the unique anaesthesia induction and maintainance was performed. Patients received 2 mg/kg propofol, 0.5 μg/kg fentanyl and 0.3 mg/kg atracurium on induction. Anaesthesia was maintained with 3% in 50% oxygen and 50% N_2O mixture. The patients whose systolic blood pressure and heart rate increased above 20% of control levels were excluded and referred to as insufficient anaesthesia. The sedation was deepened by an additional dosage of 25 μg fentanyl and by increasing sevoflurane to 4%.

BIS scores were recorded at 5-min intervals after induction and during the operation. After assessing all variables, cases were assigned to three groups according to estradiol levels. In Group 1 (n: 17) estradiol level was at or under 100 μg/dl, in Group 2 (n: 14) levels were between 100 and 200 μg/dl and finally in Group 3 (n: 13) levels were above 200 μg/dl.

One-way ANOVA, Waller-Duncan, Tukey HSD, LSD (least significant difference) and Bonferroni tests were used for staytistical analyses of BIS score during the procedure according to control levels.

Results

Forty-four female patients were evaluated in the study and placed in three groups: Group 1 had estradiol levels < 100 μg/dl, Group 2 between 100 and 200 μg/dl, and Group 3 > 200 μg/dl. Estradiol levels were found to be 59.94 ± 23.59 μg/dl ± SD in Group 1, 138.60 ± 23.49 μg/dl ± SD in Group 2 and 239.30 ± 41.08 μg/dl ± SD in Group 3.

There were 17 patients in Group 1 with a mean age of 37.47 ± 5.06, 14 patients in Group 2 with a mean age of 33.71 ± 6.60, and 13 patients in Group 3 with a mean age of 34.30 ± 7.23 (years ± SD). The groups were similar with respect to age, sex and duration of the operation (Table 1).

Table 1. — *Patient range of age, weight, and operation duration according to groups.*

	Age *(years ± SD)*	Weight *(kg ± SD)*	Operation duration *(min ± SD)*
Group 1 (n: 17)	37.47 ± 5.06	70.47 ± 12.03	40.35 ± 3.20
Group 2 (n: 14)	33.71 ± 6.60	64.00 ± 10.26	42.78 ± 4.99
Group 3 (n: 13)	34.30 ± 7.23	72.30 ± 7.53	43.69 ± 4.36
p values	*0.208*	*0.096*	*0.506*

Diagnostic laparoscopy and laparoscopic tubal ligation were the procedures most performed during the study. Operation types are shown in Table 2.

A significant difference in BIS levels was not observed between control and post-induction levels. However the values between 10 and 80 min changed significantly ($p < 0.0001$) (Table 3, Figure 1). A similar significance was observed in Waller-Duncan, Tukey HSD, LSD and Bonferroni tests ($p < 0.0001$).

MAP ve SpO_2 did not change significantly in relation to control levels.

Table 2. — *Type of surgery.*

Operation	Number
Diagnostic laparoscopy	18
Laparoscopic tubal ligation	15
Repair of stress incontinance	5
Repair of cystocele	3
Total abdominal hysterectomy	2
Repair of rectocele	1
Total	*44*

Table 3. — *Patient BIS values according to control, induction and 10-80 min means of procedures.*

	BIS		
	Control	Post induction	Mean of 10-80 min.
Group 1 (n: 17)	93.61 ± 3.27	43.69 ± 4.36	48.87 ± 3.76
Group 2 (n: 14)	94.57 ± 3.00	42.78 ± 4.99	42.12 ± 4.23
Group 3 (n: 13)	93.05 ± 4.02	40.35 ± 3.20	33.99 ± 2.30
p values	*0.494*	*0.085*	*< 0.0001*

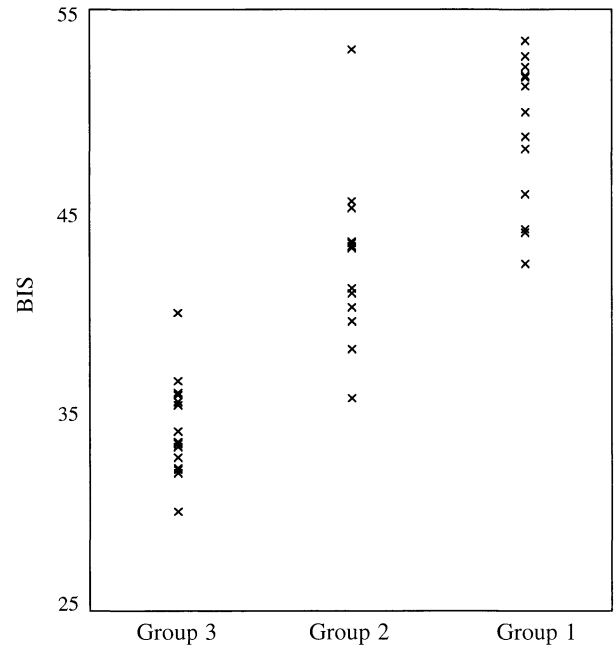

Figure 1. — Range of 1-80 min means of BIS valus

Discussion

Synaptically located transmitter-gated ion channels are now considered prime targets of general anaesthetic action [7]. Some general anaesthetics are highly selective for particular members of this receptor superfamily. Gamma aminobutyric acid (GABA) is involved with sensory processing throughout the central nervous system (CNS), including processing of nociceptive information at the level of the spinal cord [8]. It is known that $GABA_A$ and NMDA receptors are important sites of general anaesthetic actions [9-12]. The density of these receptors in the cerebral cortex is higher than in most other parts of the central nervous system. Furthermore, a role of cortical $GABA_A$ receptors in hypnosis has also been suggested by the action of sedative drugs [13]. Activation of GABAA receptors produces either hyperpolarization or

depolarization of neurones resulting in presynaptic or postsynaptic inhibition [13]. The $GABA_A$ receptor is a pentameric ligand-gated chloride ion channel with binding sites for GABA and separate modulatory sites for barbiturates, benzodiazepines, propofol and neurosteroids [14, 15]. Intrathecal injection of water soluble amino-steroid anaesthetics has been shown to cause antinociception in rats, which was a result of interaction of the drugs with spinal cord $GABA_A$ receptors [16].

A combination of alphaxalone and alphadolone (Althesin, Alfathesin) was first used in a clinical trial in 1970 in England [17]. It became popular in the entire world except the USA but went out of routine practice due to bronchospasm and anaphylactic reactions [18-24]. The combination of alphaxalone and alphadolone is a good induction agent with minimal cardiovascular side-effects and a rapid recovery rate. It also has minimal cumulative effects, which led to its use as an infusion both for anaesthesia and sedation [25]. It was concluded that althesin caused cerebral metabolic depression which was accompanied by decreased CBF and increased VCR [26].

Imaging studies on human subjects demonstrated that some general anaesthetics strongly depress cortical metabolism and blood flow [27, 28]. This general decrease in metabolic activity is believed to reflect the reduced synaptic activity across the brain in the anaesthetic state. BIS technology is the first practical neurophysiological monitoring system that provides continuous documentation of CNS depression during anaesthesia. Specifically, the BIS Index provides a measurement of the hypnotic effect of anaesthesia. As such, it functions as an early indicator of changes in brain effects due to anaesthetic dosing and delivery [29]. Excessive anaesthetic administration may be unnecessary or even harmful if cases have high estradiol levels. In such cases, administration of excessive anaesthetic must be avoided. Anaesthesists should be alert in serum estrogen elevated cases such as polycystic ovarian syndrome and also exogenous estradiol administered cases if BIS monitering is not in practice.

It has been demonstrated that spike wave discharge in EEG is not developed by estradiol [30]. Becker *et al.* pointed out that gross electrical activity alterations in the brain are recorded owing to ovarian hormonal variation [31]. Similar effects may be confirmed for other steroid hormones. These results demonstrate that the gross electrical activity of the brain changes in parallel with changing hormone levels. The common underlying mechanism may be an activation of CNS monoaminergic pathways which are known to be involved in steroid feedback. In this study, BIS monitering showed deeper sedation levels in 200 µg/dl and higher estradiol levels.

Anaesthetic consumption showed a decreased tendency in high estradiol cases in our study. Deep anaesthesia may be demonstrated by clinical features and also by using BIS monitering. Anaesthesia monitoring is especially important to prevent deep anaesthesia in long-lasting procedures. Haemodynamic instability owing to inadequate crystalloid or erythrocyte transfusion in such cases is considered as an index of light anaesthesia. Finally this cascade may result in awareness or controversially too much drug delivery. In conclusion, perioperative morbidity and mortality incidence increases. Bispectral-index guided anaesthesia can prevent complications owing to deep anaesthesia and may measure the interaction between steroids and anaesthetics. We concluded that advanced clinical series should be performed to fully define the relationship between estradiol levels and anaesthesia depth.

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