Prurigo Reduces Propofol Requirement under General Anesthesia

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ABSTRACT
Studies, including fMRI, show that neurodegeneration or a decrease in neuron count occurs in certain brain regions of patients with chronic itchy lesions. In these studies attention was also drawn to increased GABA receptor sensitivity.

In 3 patients suffering from chronic stress-induced non-histaminergic pruritus for more than 6 weeks, who underwent elective orthopedic surgery under total intravenous general anesthesia with bispectral index monitoring, it has been determined that total propofol consumption was 50, 78 and 58 micrograms/kg/min respectively. All three operations lasted more than 2 hours, were completed without any complications or awareness and all 3 patients were hemodynamically stable among the operation. From this point of view, we observed that GABA receptor sensitivity increased in patients with chronic itching. Also the need for propofol during general anesthesia, which acts on GABA receptors, decreased to doses equivalent to average sedation doses. We consider that administering drugs acting on these receptors at optimum doses (using EEG-based monitoring) is important for patient safety especially in patients with chronic itching.

Keywords: General anesthesia, neurodegeneration, patient safety, propofol, prurigo.

I. INTRODUCTION
Prurigo nodularis is a chronic inflammatory skin disease characterized by severe pruritic and symmetrically distributed skin lesions (Fig. 1).

Two different peripheral and spinothalamic pathways for itching have been discovered: the histaminergic pathway and the non-histaminergic pathway [1]. The ‘itch-specific areas’ in the human brain are believed to be the precuneus and the posterior cingulate cortex (PCC).

II. METHODS
We report a series of 3 cases suffering from chronic stress-induced non-histaminergic pruritus for more than 6 weeks, who underwent elective orthopedic surgery under total intravenous general anesthesia with bispectral index monitoring. We aim to focus on the reduced propofol requirement under general anesthesia in this group of patients.

III. RESULTS
A. Case 1
A 49 years old female patient, weighing 80 kg with a body mass index (BMI) of 31.6 kg/m<sup>2</sup> suffering from prurigo nodularis has undergone a total knee replacement operation under general anesthesia. Her physical status was grade II according to the American Society of Anesthesiologists (ASA) and she had active skin lesions (Fig. 1). The patient’s skin lesions which were symmetrical itchy nodular lesions on the forearms and legs, especially on the extensor surfaces for 3 months, were evaluated as prurigo nodularis linked to anxiety and stress, and topical lidocaine and antibiotic pomade were started 2 weeks preoperatively. The patient was not using any systemic medications and in physical examination, she had neither a malignancy nor a chronic disease.

Anesthesia was induced with propofol, rocuronium, and fentanyl boluses. Anesthesia was maintained with propofol and remifentanil (25-50 mcg/kg/min; 1 mcg/kg/min) both titrated to keep Bispectral index (BIS) levels between 40–60 and burst suppression rate (BSR) between 0-2%. During the 2-hour operation, a total of 450 mg of propofol, 100 mg of rocuronium, 50 micrograms of fentanyl, and 700 micrograms of remifentanil were administered. It was found that the propofol dose was reduced by 50% compared to TIVA doses administered in general practice to normal individuals, intraoperative vital signs remained stable, and there was no awareness in the postoperative period (Fig.1). Sugammadex 4 mg/kg was administered as a reversal agent.

B. Case 2
45 years old, 80 kg, BMI: 31.2, ASA I status, female patient. For 20 years, there were symmetric itchy nodular lesions on the extensor surfaces of the upper arm and the back, which were induced by stress. It was evaluated as prurigo nodularis in dermatology consultation. Active skin lesions are present. She does not use any systemic or local drugs. There wasn’t any malignancy, chronic kidney disease,
or rheumatologic disease detected in the patient. Prurigo is thought to be linked to anxiety and stress. The patient underwent knee arthroscopy under general anesthesia. In addition to standard monitoring, bispectral index (BIS) monitoring was used to measure the depth of anesthesia. After induction with propofol, remifentanil, and rocuronium, maintenance was provided with total intravenous anesthesia (TIVA). During the operation, which lasted 2 hours, 80 mg of rocuronium, 75 micrograms of fentanyl, 800 micrograms of remifentanil, and propofol were used as 150 mg in induction and 500 mg in maintenance in total, keeping BIS values between 40-60. It was determined that the maintenance dose of propofol throughout the operation, which lasted for 1 hour and 20 minutes, was 78 mcg/kg/min on average. It was determined that the need for TIVA propofol dose decreased by 25-50% compared to the dose of TIVA propofol administered to normal individuals, the intraoperative hemodynamic findings were stable (Fig. 2 and 3) and awareness did not occur. Sugammadex was used at 4 mg/kg as reversal agent.

C. Case 3

A male patient aged 67 years, 94 kg, BMI: 30, ASA II status, diagnosed with chronic idiopathic urticaria, underwent hip replacement operation under general anesthesia. The patient has urticarial lesions on the head, neck and trunk. He has not been taking antihistamine treatment for 1 month. The patient stated that waking up after the previous appendectomy operation was very long and difficult, and he did not want to receive general anesthesia. The patient underwent total hip replacement surgery under general anesthesia. In addition to standard monitoring, bispectral index (BIS) monitoring was used to measure the depth of anesthesia. After induction with 180 mg propofol, remifentanil and rocuronium maintenance was provided with total intravenous anesthesia (TIVA). During the operation, which lasted 132 minute, 90 mg rocuronium, 100 micrograms of fentanyl, 850 micrograms of remifentanil and propofol were used as 150 mg in induction and 700 mg in maintenance in totally, keeping BIS values between 40-60. It was determined that the maintenance dose of propofol throughout the operation, which lasted for 2 hour and 12 minutes, was 58 mg/kg/min on average. It was determined that the need for TIVA propofol dose decreased by 25-50% compared to the dose of TIVA propofol administered to normal individuals, the intraoperative hemodynamic findings were stable and awareness did not occur. The recovery time was 4 minutes without any complication. Sugammadex was used 4 mg/kg for reversal agent (Fig. 4).

![Fig. 1. Case 1. The simmetrical nodular lesions of the prurigo nodularis patient’s legs with permission of the patient.](image1)

![Fig. 2. Intraoperative anesthetic management of the non-histaminergic itchy patient. Reduced propofol needings (30 mg/h) and the bispectral index status of the patient.](image2)

![Fig. 3. Intraoperative anesthetic management of the chronic idiopathic urticaria patient. Reduced propofol (28 mg/h infusion rate) needings and the bispectral index status (Sedline value 30-34) of the patient. Figure shows the patient’s haemodinamical stability throughout the operation.](image3)

![Fig. 4. Intraoperative anesthetic management of the chronic idiopathic urticaria patient.](image4)

IV. DISCUSSION

Studies have shown that the core areas in the brain activated by histaminergic and nonhistaminergic stimuli are the thalamus, primary and secondary somatosensory cortices, posterior parietal cortex, superior and middle temporal cortices, (PCC), anterior cingulate cortex (ACC), precuneus, and cuneus [2].

Two distinct peripheral and spinothalamic pathways have been discovered for pruritus: the histaminergic and the nonhistaminergic pathway [1].

The ‘itch-specific areas’ are believed to be precuneos and PCC. These areas can be activated by an itchy stimulation [3].

Non-histaminergic pruritus, are separate from the pathway induced by histaminergic pruritus, and subsequent spinothalamic pathways have also been found to be different [4], [5].

Since the thalamus is largely activated by the nonhistaminergic pruritus, these stimuli have been shown in studies to cause a strong activation of the PCC, posterior parietal cortex, prefrontal cortex (PFC) and precuneus [6]. Pruritic end-stage kidney disease patients have more
activation and increased gray matter density in the amygdala, hippocampus compared to healthy controls [7].

In patients with prurigo nodularis or lichen simplex chronicus, hipppocampal activation is significantly increased during stress-induced pruritus [8].

The inhibitory activity of gamma-aminobutyric acid (GABA) is divided into 2 main types. Phasic inhibition and tonic inhibition. Tonic GABAergic inhibition has been demonstrated in the mammalian brain, particularly the hippocampus, the thalamocortical neurons of the ventral basal complex, and the neocortex [9], [10].

It has been shown that 75% of all inhibitory stimuli in hippocampal neurons are tonic inhibition. The effect of propofol, midazolam, etomidate and gaboxadol on tonic inhibition is observed to be several times greater compared to synaptic phasic inhibition. The extrasynaptic concentration of GABA does not fully saturate of GABA receptors. An increase in agonist affinity by anesthetics can greatly increase GABAergic current.

Propofol (2,6-diisopropylphenol) is a short-acting intravenous (i.v.) sedative-hypnotic agent. It directly activates GABAA receptors. Inhibits N-methyl-d-aspartate (NMDA) receptor and also modulates calcium influx through slow calcium ion channels [11].

Propofol prolongs inhibitory postsynaptic currents mediated by GABA receptors. Propofol also affects the presynaptic mechanisms of GABAergic transmission. It is extensively metabolized in the liver via the cytochrome P450 system and glucuronidation. [12].

Researchers observed the effect of propofol on noradrenaline in the human brain function with fMRI, and showed that the decrease of signals in the hypothalamus, frontal lobe and temporal lobe was significantly correlated with propofol anesthesia. They suggested that these brain regions are susceptible to propofol anesthesia [13].

Chronic itching in the brain (over 6 weeks) can alter functional brain connections in the ACC, PCC, PFC brain areas. It can reduce gray matter in cortical areas associated with itching PFC and precuneus.

Gamma-aminobutyric acid (GABA) analogs are very effective in the treatment of neuro-pathic forms of itch. The mechanism is probably a reduction in central neural hypersensitization [14], [15].

Our suggestion is neuronal loss of this GABAergic interneurons or neurons may lead to increase the extrasynaptic GABAergic activity /sensitivity under low concentrations of this neurotransmitter. This supports our argument for GABAergic neuron loss or high sensitivity/modified GABAergic current in chronic itch.

Common features in all 3 of our cases are that they have active itchy lesions lasting longer than 6 weeks, no other co-morbidities, and not taking systemic antihistamine treatment for at least 1 month. Apart from these patients, it was determined that a male patient with chronic urticaria used antihistaminic agent until 1 day before the operation. During the operation, it was observed that the propofol infusion dose required to keep the bispectral index values between 40-60 and the burst suppression rates to be at the level of 0-2% increased up to 150-200 mcg/kg/min, and the propofol requirement was at the level of normal adult general anesthesia doses. Studying the situation, we observed in more patient groups and supporting it with fMRI studies will clarify the decreased propofol requirement in this patient group, which we claim. At the same time, the basal, fully awake bispectral index and sedline values of all our patients were recorded and their EEG activities were observed. The aim here is to rule out abnormal BIS values in some patients. (BIS <60 with awake patient and awake looking EEG; BIS >60 with an unconscious patient and awake looking EEG; BIS 60< with an awake patient but an asleep looking EEG)

We tried to draw attention to this phenomenon by sharing our observation is degeneration of GABA interneurons decrease inhibition to nociceptive pathway and contribute to hypersensitivity. As a result of this hypersensitivity decreased propofol need occurs during anesthesia, which we previously claimed in cases with narcolepsy, chronic urticaria and essential tremor. [16]-[18]

On the other hand, mounting evidence suggests that propofol inhibits and interferes with multiple enzymes and components within the electron transport chain and disrupts fatty acid oxidation. Recent studies showed that toxic concentrations of propofol uncoupled immature cardiomyocyte mitochondria by inducing a dose-dependent increase in proton leak.

In this patient group, it is observed that propofol dose adjustments are required at levels that will keep the burst suppression rates low (0-2%). Because high burst suppression rates will lead to low ATP levels in these highly affected neuron groups and increase neuron losses, including those in the postoperative period. In fact, it is quite possible to prepare the ground for the development of postoperative delirium.

V. CONCLUSION

We suggested that GABA receptor sensitivity increased in patients with chronic itching. Also, the need for propofol during general anesthesia, which acts on GABA receptors, decreased to doses equivalent to average sedation doses.

A. State of Knowledge on the Subject

Studies conducted in chronic pruritic conditions have shown an increase in GABA receptor activity. There are also studies in the literature on which brain regions have neuronal losses with these conditions. However, no study has been found on the decrease in the propofol requirement of such patients in anesthesia practice.

B. Contribution of Our Study to the Knowledge

Administering drugs acting on these receptors at optimum doses (using EEG-based monitoring) is important for patient safety especially in patients with chronic itching.

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CONFLICT OF INTEREST

Authors declare that they do not have any conflict of interest.
REFERENCES


