

Kentaro Ouchi*

Department of Dental Anesthesiology, Assistant professor, Field of Maxillofacial Diagnostic and Surgical Sciences, Faculty of Dental Science, Kyushu University, Graduate School, Japan

Dates: Received: 14 October, 2015; Accepted: 15 October, 2015; Published: 15 October, 2015

*Corresponding author: Kentaro Ouchi, DDS, PhD, Department of Dental Anesthesiology, Field of Maxillofacial Diagnostic and Surgical Sciences, Faculty of Dental Science, Kyushu University Graduate School, 3-1-1 Maidashi, Higashi-ku, Fukuoka 812-8582, Japan, Tel: +81-92-641-1151; Fax: +81-92-642-6481; E-mail: ken2006anes@yahoo.co.jp

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Editorial

Intravenous General Anesthesia for Patients with Neurological Disorders

Editorial

In dental practice, intravenous general anesthesia is useful for patients who are difficult to treat when not sedated such as those with neurological disorders [1].

Monitoring

A bispectral index sensor (BIS) was attached to the patient's forehead and connected to a BIS monitor (Aspect Medical Systems Inc.) to evaluate the level of intravenous general anesthesia. BIS is nonessential but helpful. In intravenous anesthesia without BIS, observation of sedation score is necessary, more precisely. Pulse oximetry sensor placed on the patient's digit. Pulse oximetry is usually used for monitoring of respiratory function during intravenous anesthesia. However, it has certain limitations. Under anesthesia with oxygen supplementation, the decrease in pulse oxygen saturation may be delayed despite severe respiratory insufficiency [2,3]. Respiratory rate measurement involved use of an adhesive sensor, including an acoustic transducer (Masimo Corp., Tokyo, Japan), placed on the patient's throat, on the side of the larynx and above the thyroid cartilage. The sensor allows real time analysis of the vibrations emanating from the patient's larynx and enables isolation of the respiratory sounds via analysis of the trace obtained through various filters. The acoustic signal is then converted to a numerical value, allowing a continuous display of the respiratory rate value. Respiratory rate measurement is nonessential but helpful. In intravenous anesthesia without respiratory rate measurement, observation of oxygen saturation and movement of the chest by the breathing is necessary, more precisely.

Intravenous general anesthesia protocol

Oxygen supplied through nasal cannula. Nitrous oxide (approximate concentration, 20%) can also be used together for oxygen supplementation. Intravenous general anesthesia was induced and maintained with continuous infusion of propofol. Using a propofol TCI pump (Graseby Medical Ltd., Hertfordshire, UK, or Terumo Co., Tokyo, Japan) with a built-in TCI system (Diprifusor, AstraZeneca Plc., London, UK) and according to the parameters reported by Marsh [4], continuous intravenous infusion of propofol

was initiated using the TCI method. The dose of propofol was titrated to achieve a BIS of 50 and achieve an adequate level of anesthesia: asleep but not responding to stimulation. Endotracheal intubation was not performed, and spontaneous breathing was maintained. The level of anesthesia was maintained at BIS 30-50 by adjusting the target propofol level using TCI (Figure 1). Without BIS, The dose of propofol was titrated to achieve a Mackenzie Grant score of 5 and to achieve an adequate level of anesthesia: asleep, but not responding to stimulation. The level of anesthesia was maintained at a Mackenzie and Grant score of 5 by adjusting the target propofol level using the propofol TCI (Figure 2). If respiratory depression was observed or BIS value was less than 30, the target blood concentration of propofol was decreased by 0.2 µg/ml. If the anesthesia level was deemed inadequate BIS value was more than 50, the target blood level of propofol was increased by 0.2 µg/ml. The dental procedure was started after the anesthesia level became stable without respiratory depression. A local anesthetic was used appropriately by the operating dentist. Administration of propofol was discontinued at the end of the dental procedure. Patients were monitored until recovery from anesthesia, when they were fully awake and had stable respiration.

Antiepileptics affect for anesthesia

Patients with intellectual disabilities need higher doses of sedatives than those without intellectual disabilities to obtain an adequate level of anesthesia [5]. Among patients with neurological disorders, those with intellectual disabilities suffice with lower doses of sedatives to obtain an adequate level of anesthesia compared to patients with autism [6]. Many of neurological disorders patients have epilepsy and are medicated with antiepileptic drugs. In these

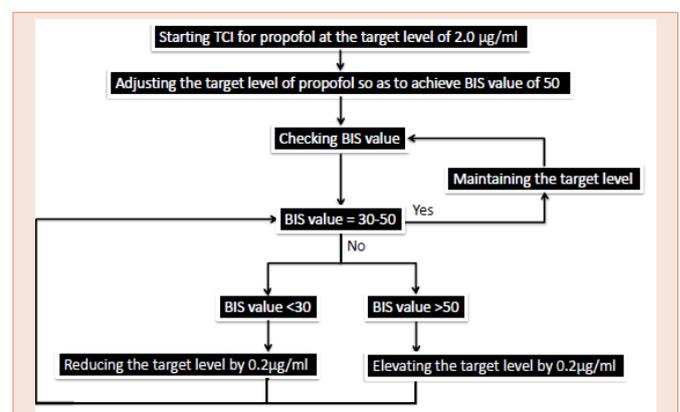


Figure 1: Intravenous general anesthesia protocol with BIS. TCI: target-controlled infusion. BIS: Bispectral index.

reports, the group with lower doses of sedatives to obtain an adequate level included those who were given an antiepileptic. In patients not given an antiepileptic, there were no differences in the required dose of propofol and emergence among patients with autism, cerebral palsy, and intellectual disability [7]. It reported that propofol dose required for anesthesia and the emergence time from anesthesia are affected by antiepileptic use [7].

Metabolic reactions are catalyzed by cytochrome P450 (CYP) and uridine diphosphate glucosyltransferase (UGT) enzymes. CYP2B6, CYP2C9, and CYP2C19 contribute to the metabolism of propofol [8-10]. Certain antiepileptic drugs increase the blood concentration of propofol by inhibiting the action of CYP and UGT [7].

Hepatic enzyme inhibition usually occurs because of competition at the enzyme site and results in a decrease in the rate of metabolism of the affected drug [11,12]. Thus, certain antiepileptic drugs have been increased the blood concentration of propofol by inhibiting the action of CYP and UGT. Carbamazepine contributes to the competitive inhibition of hepatic CYP2C9, because metabolism CYP is the same as propofol. (7) In addition, carbamazepine inhibits 2C19 [13]. Topiramate inhibits CYP2C19, in clinical study [14]. Valproate contributes to the competitive inhibition of CYP2B6, because metabolism CYP is the same as propofol [7]. In addition, valproate inhibits CYP2C9 *in vitro* [15]. And valproate inhibits UGT 1A9, which mediates glucuronic acid conjugation, the main metabolic pathway of propofol [16,17]. Phenobarbital contributes to the competitive inhibition of hepatic CYP2C9, because metabolism CYP is the same as propofol. In addition, phenytoin inhibits CYP2C9, clinically [14,18]. And, *in vitro*, phenytoin, phenobarbital, and valproate inhibit UGT 1A9, which mediates glucuronic acid conjugation, the main metabolic pathway of propofol [16,17]. Benzodiazepine as clobazam contributes to the competitive inhibition of hepatic CYP3A4 and CYP2C19, because metabolism CYP is the same as propofol [19]. In addition, benzodiazepines such as diazepam and clobazam have sedation effect through GABA-A receptor [20,21]. Therefore, by these mechanisms, antiepileptic drugs such as carbamazepine, valproate, phenytoin, benzodiazepine and topiramate reduce the required dose of propofol and extend the time needed for emergence from anesthesia.

In contract, the propofol metabolism may be no affected by the use of phenobarbital and zonisamide. Phenobarbital inhibits UGT 1A9, *in vitro* [17,22]. But, phenobarbital induces CYP2C19 [23]. Thus, phenobarbital induces and inhibits the metabolism of propofol. Consequently, because inducement and inhibition compete, phenobarbital may not affect the metabolism of propofol. Hepatic enzyme inhibition usually occurs because of competition at the enzyme site and results in a decrease metabolism of the affected drug [11,12]. Thus, it may suppose that zonisamide contribute to the competitive inhibition of hepatic CYP2C19 that is the same as propofol, because principal inactivation pathways of zonisamide is CYP3A4, CYP2C19 and CYP3A5 [24]. But, it is reported that zonisamide does not induce or inhibit the metabolism of other drugs that included drugs metabolize by CYP3A4 or CYP2C19 [25]. Therefore, zonisamide may not affect the metabolism of propofol.

Therefore, propofol metabolism is affected by antiepileptic use,

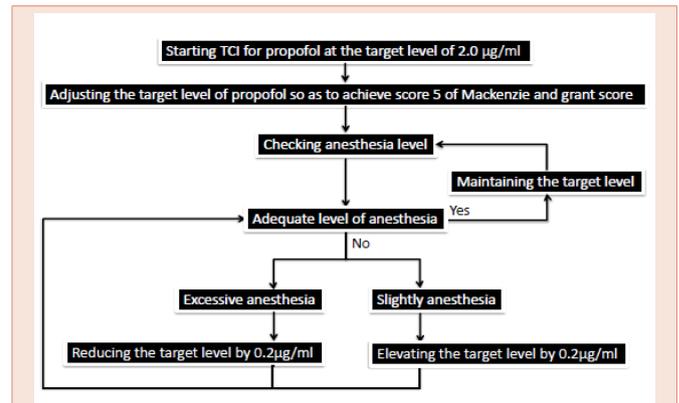


Figure 2: Intravenous general anesthesia protocol without BIS.

TCI: target-controlled infusion.

Mackenzie grant score; 1, Fully awake; 2, Drowsy; 3, Eyes closed but rousable to command; 4, Eyes closed but rousable to mild physical stimulation; 5, Eyes closed and unrousable to mild physical stimulation

Table 1: Affect for propofol metabolism.

Antiepileptic	Affect for propofol metabolism
Carbamazepine	Inhibit
Valproate	Inhibit
Phenobarbital	Induce / Inhibit
Phenytoin	Inhibit
Zonisamide	No affect
Benzodiazepine	Inhibit
Topiramate	Inhibit

and is affected by the type of antiepileptic (Table 1). Consequently, in intravenous anesthesia for patients with epilepsy, required propofol dose is lower, emergence from anesthesia is delayed.

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