



## The Concentration for Loss of Consciousness by Propofol does not differ between Morning and Afternoon

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### Abstract

**Background:** Circadian rhythms influence the pharmacology and effects of anesthetic agents such as local anesthetics, general anesthetics, and muscle relaxants. However, the influences of the circadian rhythm on new anesthetics such as propofol are unknown.

**Method:** Propofol, one of popular intravenous anesthetics, was administered intravenously using the Diprifusor™ system, which is a target-controlled infusion system of propofol. The propofol infusion started with an initial effect-site concentration of 4 $\mu$ g/mL for 3 min and increased in increments of 0.5 $\mu$ g/mL every 30 sec after the first 3 min until the patient lost the eyelash reflex and exhibited no response to verbal commands. The predicted blood concentration and the predicted effect-site concentration of propofol required for loss of consciousness (LOC) were recorded.

**Results:** Thirty-seven patients underwent induced anesthesia at 8:30. Twenty-eight patients were induced between 14:00 and 16:00. There was no significant difference between the two groups in the predicted blood concentration, the predicted effect-site concentration and the time for LOC.

**Conclusion:** The concentration for LOC by propofol is not influenced by the time of day, at least during the human active period.

### Keywords

Circadian rhythm, Effect-site concentration, General anesthesia, Loss of consciousness, Propofol

### Introduction

Biologic rhythms in blood pressure, immune system activities, blood coagulation, hormones release, gastric function, and renal function influence mammalian bodies throughout the day [1,2]. In the central nervous system, the circadian rhythm pacemaker is in the suprachiasmatic nucleus of the hypothalamus, and the main synchronizer is light [1,2]. Drugs influence biological rhythms, and the time when they are administered influences their effects [1,2]. The efficacy and toxicity of many local anesthetics in humans reportedly depend on their administration time [1,2]. Some general anesthetics such as halothane, pentobarbital, diazepam, and midazolam also show circadian changes in their efficacy and toxicity in rodents and

in humans [1,2]. However, the influences of the circadian rhythm on new anesthetics such as propofol are unknown. It has been reported that the duration of the loss of the righting reflex in rats is longer during the light phase than during the dark phase [3]. There is no similar finding in humans. In the present study, we investigated the propofol concentration at loss of consciousness (LOC) at different times.

### Methods

This study was approved by the Ethics Committee of Gifu University Graduate School of Medicine (Gifu, Japan), and was registered in the University Hospital Medical Information Network in Japan (Tokyo, Japan; registration number: UMIN000011252). All patients provided written informed consent. We recruited patients who were 20-49 years old and American Society of Anesthesiologists physical status 1. All patients were women who were planned to undergo an operation under only general anesthesia between January 2013 and August 2014. The exclusion criteria were as follows: pregnancy, neurologic and psychiatric disease, use of anxiolytics medications, use of antidepressants or opioids, use of hypnotics before the night of operation, and a body mass index over 30. On arrival to the operating room, the patients were monitored by noninvasive arterial blood pressure, electrocardiogram, pulseoximetry and Bi-Spectral Index (BIS) monitor. After baseline hemodynamic profiles were obtained, supplemental oxygen (6 L/min) was administered through a facemask. Propofol was administered intravenously using the Diprifusor™ system (TE-371; Terumo, Tokyo Japan), which is a target-controlled infusion system of propofol, through an intravenous catheter placed in the patients' forearm. This delivery system regulates the infusion rate automatically for the goal blood concentration calculated from the target effect-site concentration and displays the predicted blood concentrations and the predicted effect-site concentrations (i.e., the drug concentration at site of action) as estimated by Marsh's pharmacokinetic model. The propofol infusion started with an initial effect-site concentration of 4 $\mu$ g/mL for 3 min and increased in increments of 0.5 $\mu$ g/mL every 30 sec after the first 3 min until the patient lost the eyelash reflex and exhibited no response to verbal commands. This clinical endpoint was defined as "loss of consciousness" and was assessed

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**Table 1:** Patients' characteristics and physiology

Time of induction	8:30 (n = 37)	14:00-16:00 (n = 28)
Age (y)	37.2 ± 8.1	35.6 ± 7.0
Height (cm)	166.3 ± 4.3	157.3 ± 3.9
Weight (kg)	52.0 ± 6.9	51.1 ± 4.8
Baseline BIS value	97.5 ± 0.7	97.2 ± 1.0

The data are expressed as the mean ± the standard deviation.

BIS: Bi-Spectral Index

**Table 2:** The predicted blood and the predicted effect-site concentration, BIS value and time for loss of consciousness

Time of induction	8:30	14:00-16:00
Blood concentration (μg/mL)	4.5 ± 0.8	4.5 ± 0.6
Effect-site concentration (μg/mL)	2.1 ± 0.7	2.1 ± 0.8
BIS value	52.1 ± 12.9	49.9 ± 12.4
Time (sec)	171.1 ± 71.3	171.4 ± 70.9

The data are expressed as the mean ± the standard deviation.

BIS: Bi-Spectral Index

every 15 sec during the induction of anesthesia. The predicted blood concentration and the predicted effect-site concentration of propofol required for LOC were recorded.

## Statistical Analysis

The patients' characteristics, the propofol concentration, and the time needed for LOC in the two groups were analyzed by the unpaired Student *t*-test. A value of *P*<0.05 indicated a statistically significant difference.

## Results

In our hospital, many patients were scheduled for their operation at 8:30 or between 14:00 and 16:00 (both times are at light phase). Therefore, we compared these two groups, based on the start time of general anesthesia. Thirty-seven patients underwent induced anesthesia at 8:30. Twenty-eight patients were induced between 14:00 and 16:00. **Table 1** presents the patients' characteristics. The two groups were similar in age, weight, height, and baseline BIS. In the patients who underwent induced anesthesia at 8:30; the predicted blood concentration of propofol at LOC was 4.5 ± 0.8 μg/mL; the predicted effect-site concentration of propofol at LOC was 2.1 ± 0.7 μg/mL; the BIS value at LOC was 52.1 ± 12.9; and they required 171.1 ± 71.3 sec for LOC. In the patients who underwent induced anesthesia between 14:00 and 16:00; the predicted blood concentration of propofol at LOC was 4.5 ± 0.6 μg/mL; the predicted effect-site concentration of propofol at LOC was 2.1 ± 0.8 μg/mL; the BIS value at LOC was 49.9 ± 12.4; and they required 171.4 ± 70.9 sec for LOC (**Table 2**). There was no significant difference between the two groups in the predicted blood concentration, the predicted effect-site concentration, BIS value and the time for LOC.

## Discussion

Circadian rhythms influence the pharmacology and effects of anesthetic agents such as local anesthetics, general anesthetics, and muscle relaxants [1,2]. Many general anesthetics such as pentobarbital, propofol, and ketamine obtain the maximum hypnotic effect during the rest phase in animals, which corresponds to the night time in humans [1,2]. When the general anesthetics concentrations for LOC differ by the time of day, the concentrations required for maintaining general anesthesia may be different. At the present time, we can regulate anesthesia depth by monitoring BIS, entropy, or other methods. However, it is necessary to know the influence of the circadian rhythm on the effect of anesthetic agents. The duration of the loss of the righting reflex after propofol administration in rats is reportedly longer during the light phase (i.e., rest period) than during the dark phase (i.e., active period) [3]. On the other hand, the duration of the loss of the righting reflex in mice is longer in the dark phase (i.e., active period) than in the light phase (i.e., rest period) [4].

No human study has been performed to demonstrate that the effect of propofol is affected by the circadian rhythm. It is well known that propofol binds to the type A gamma-amino butyric acid (GABA<sub>A</sub>) receptors in neurons [5]. It has been reported that the sensitivity of GABA<sub>A</sub> receptors in the suprachiasmatic nucleus changes between day and night [6]. Therefore, we investigated the concentration for LOC by propofol at two different times in humans. However, the time of day of propofol administration start did not influence the concentration for LOC in women. In the present study, we choose the times of 8:30 and between 14:00 and 16:00 because many patients in our hospital are scheduled for an operation at these times. Because both times are within the active period in humans and within the light phase in our country, it may be that the concentration for LOC was not influenced by the time of propofol administration.

In addition, we administered propofol using the Diprifusor™ system, which calculates the effect-site concentration based on Marsh's pharmacokinetic model. This model calculates the effect-site concentration based on the patient's weight, whereas Schnider's pharmacokinetic model calculates the effect-site concentration based on the patient's weight, age, height, and lean body mass. The target-controlled infusion system administers propofol more rapidly by the Marsh model than by the Schnider model [7]. Therefore, it is possible that there are differential results in the concentration for LOC when using a target-controlled infusion system that is based on Schnider's model.

## Conclusion

The concentration for LOC by propofol is not influenced by the time of day, at least during the human active period.

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