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Individual Effect-Site Concentrations of Propofol are Similar at Loss of Consciousness and at Awakening

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Abstract

Reported effect-site concentrations of propofol at loss of consciousness and recovery of consciousness vary widely. Thus, no single concentration based on a population average will prove optimal for individual patients. We therefore tested the hypothesis that individual propofol effect-site concentrations at loss and return of consciousness are similar. Propofol effect-site concentrations at loss and recovery of consciousness were estimated with a target-control infusion system in 20 adults. Propofol effect-site concentrations were gradually increased until the volunteers lost consciousness (no response to verbal stimuli); unconsciousness was maintained for 15 minutes, and the volunteers were then awakened. This protocol was repeated three times in each volunteer. Our major outcomes were the concentration producing unconsciousness and the relationship between the estimated effect-site concentrations at loss and recovery of consciousness. The target effect-site propofol concentration was 2.0 ± 0.9 at loss of consciousness and 1.8 ± 0.7 at return of consciousness ($P < 0.001$). The average difference between individual effect-site concentrations at return and loss of consciousness was only 0.17 ± 0.32 μg/mL (95% confidence interval for the difference 0.09 to 0.25 μg/mL). Our results thus suggest that individual titration to loss of consciousness is an alternative to dosing propofol on the basis of average population requirements.

Implications—Propofol can be titrated to the concentration that produces consciousness in individual patients. Provided that the propofol effect-site concentration does not much exceed the concentration initially required to produce unconsciousness, patients can be expected to awaken quickly upon completion of the procedure.

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Introduction

Plasma propofol concentrations at loss of consciousness using target-controlled infusions (TCI) of propofol for anesthesia have been reported previously (1–5); however, large differences were found between the minimum and maximum values. For example, Vuyk *et al.* (2) reported an arterial plasma concentration of 2.8 to 5.4 μg/mL, and Milne *et al*. (5) reported the effective concentration for 5% of the patients (EC_5) at loss of consciousness was 1.5 (range 1.3–1.7) μg/mL; the EC_{50} was 2.8 (2.7–2.9) μg/mL; and the EC_{95} was 4.1 (3.9–4.3) μg/mL. Doufas, *et al*. similarly report a substantial standard deviation for loss of consciousness during propofol: 1.9 ± 0.7 μg/mL (6). For returning of consciousness, the propofol at awakening was reported to be 2.7 ± 0.6 μg/mL by White, *et al* (7). In contrast, Wessen *et al*. found the concentration at awakening to be 1.1 ± 0.1 μg/mL (8).

The large variation among patients in the effect-site concentration producing unconsciousness makes it difficult to target the minimum concentration that will provide effective sedation in a given patient. This would be of little consequence if large doses were well tolerated. However, propofol-induced respiratory depression develops at very nearly the individual concentration that provokes loss of consciousness (6). There are thus compelling clinical reasons to restrict propofol administration to the minimum effective concentration — especially when the drug is being given by non-anesthesiologists, as is increasingly the case

In the absence of individual pharmacodynamic information, propofol is usually dosed on the basis of average population requirements. Using this typical clinical approach, we have observed that patients requiring large concentrations of propofol at loss of consciousness tend to recover consciousness quickly, whereas patients who lose consciousness at low propofol concentrations usually recover consciousness slowly.

This observation suggests that loss and recovery of consciousness may occur at similar effect-site concentrations of propofol within each individual. If so, this would suggest a clinical management strategy likely to work better than simply targeting a population-based average effective concentration. Specifically, propofol in individual patients could be titrated to a concentration that equals or only slightly exceeds the concentration necessary to induce loss of consciousness and subsequently be maintained at a similar concentration. We therefore tested the hypothesis that the effect-site concentration of propofol at loss of consciousness is similar to that at recovery of consciousness.

Method

With approval of the Ethics Committee at Tokyo Women's Medical University and written informed consent, we enrolled 20 healthy adult volunteers (10 men and 10 women). The volunteers refrained from food and water for approximately four hours before starting the protocol.

A Diprifusor TCI pump (Graseby 3500 pump, Graseby Medical Limited, Colonial Way, Watford, Herts, WD24 4LG, United Kingdom) was connected to an intravenous catheter in the left antecubital vein of each volunteer.

Electrodes were positioned for monitoring the electrocardiogram and the bispectral index of the electroencephalogram (BIS, A-1050-software version 3.0, Aspect Medical, Inc., Newton, MA, USA). Arterial blood pressure and arterial oxygen saturation were measured noninvasively.

Propofol was infused to a target plasma concentration of 3.0 μg/mL based on a prior report.[4] Effect-site concentration thus gradually increased as the pump ramped up towards the

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designated target concentration. Loss of consciousness was defined as the loss of reaction to calling the volunteer's name. The volunteers' names were spoken in a normal speaking volume at 30-second intervals by investigators who was blinded to effect-site propofol concentration. The volunteers were not prodded or otherwise stimulated. When loss of consciousness did not occur, even though the effect-site concentration was 3.0 μg/mL, the target concentration was increased in increments of 0.5 μg/mL until loss of consciousness occurred. All volunteers lost consciousness at a target concentration of less than 5.0 μg/mL.

With TCI, approximately 15 minutes is required for equilibrium between the plasma and effect-site concentrations (5,9). We therefore maintained the target concentration and deep sedation (BIS < 60) for at least 15 minutes after loss of consciousness. In rare cases where BIS exceeded 60, the propofol target concentration was increased by 0.5 μg/mL and the sedation period was extended an additional 15 minutes. The target concentration was subsequently set to zero, but the Diprifusor was kept "on." We defined recovery of consciousness as the time the subjects opened their eyes in response to their names being loudly called at 30-sec intervals.

After recovery of consciousness and a BIS value exceeding 90, we confirmed that the volunteers were lucid and able to articulate their birthdays, addresses, telephone number, and were able to perform simple calculations. The volunteers were then observed for 20 minutes, and the entire process "from loss of consciousness to recovery of consciousness" was repeated twice using an identical protocol. The entire loss-of-consciousness to return-of-consciousness sequence was thus performed three times in each volunteer.

For each study sequence, hemodynamic responses were evaluated before propofol administration, at loss of consciousness, at a BIS of 60, and at return of consciousness. These values were compared using repeated-measures ANOVA with Tukey-Kramer *post hoc* testing;.

The effect-site concentrations at loss and return of consciousness were compared with two-tailed, paired *t* tests. Results are presented as means ± SDs and percents; a P value < 0.05 was considered significant and adjusted for multiple comparisons when appropriate.

Results

The volunteers were 26 ± 2 years old, weighed 60 ± 11 kg, were 161 ± 24 cm tall. The studies required an average of 124 ± 18 minutes. Consciousness was lost within 5 minutes in 14 of the volunteers (70%), whereas 6 volunteers required longer (30%). There was a brief in decrease in SpO2 to 91% in a single volunteer who then recovered spontaneously; saturation otherwise exceeded 95% in all volunteers at all times. None of volunteer subjects required supplemental oxygen or assisted ventilation. As might be expected, mean arterial pressure was slightly greater without propofol than during sedation; however, the differences were only about 10 mmHg. In contrast, heart rate remained essentially unchanged throughout the study.

There was an approximately six-fold inter-individual difference between the minimum (0.7 μg/mL) and maximum effect-site concentrations (4.8 μg/mL) at loss of consciousness and at recovery of consciousness (minimum 0.8 μg/mL and maximum 4.5 μg/mL). However, the mean predicted effect-site concentrations of propofol at loss of consciousness and at recovery of consciousness were 2.1 ± 1.0 and 1.9 ± 0.7 μg/mL (P = 0.027) for the first trial, 1.9 ± 0.9 and 1.8 ± 0.8 μg/mL (P = 0.027) for the second trial, and 2.0 ± 0.9 and 1.8 ± 0.7 μg/mL (P = 0.015) for the third trial. Combining the three trials, the target effect-site propofol concentration was 2.0 ± 0.9 at loss of consciousness and 1.8 ± 0.7 at return of consciousness (P < 0.001, Fig. 1).

Although differences in effect-site concentrations at loss and return of consciousness were statistically significant, the average difference between individual effect-site concentrations at

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return and loss of consciousness was only 0.17 ± 0.32 μg/mL; the 95% confidence interval for the difference was 0.09 to 0.25 μg/mL, and hence not clinically important. Additionally, only 15% of the differences were greater than 0.5 μg/mL and only one out of 60 (2%) was greater than 1.0 μg/mL. Results were similar in men and women.

Discussion

Target-controlled infusion (TCI) systems facilitate clinical management of intravenous anesthesia by providing control of intravenous drugs analogous to that provided for potent inhaled anesthetics by vaporizers (10,11). Just as potency of inhaled anesthetics can be quantified by the minimum alveolar concentration (MAC), requirement for intravenous anesthetics is typically expressed as the effect-site concentration that provokes a given response in 50% of the population (EC50). The Diprifusor pump that we used controls propofol administration based on a three-compartment model (12) based on pharmacokinetic parameters developed by Marsh ($Ke0=0.26min^{-1}$) (13). The system is fairly precise and has an acceptable degree of bias (14,15).

A complexity of intravenous anesthetics is that drug concentration in blood may not equal the concentration at the brain effect site. A useful index for the management of intravenous anesthesia is thus the effect-site concentration (1,16,17). The importance of propofol effect-site concentration is that it correlates better with patient response than plasma concentration (3,7,8,16,18). The Diprifusor displays estimates of both plasma and effect-site concentrations. Our results are reported in terms of estimated effect-site concentrations because this is the physiologically relevant parameter. Both MAC of inhaled anesthetics and effect-site concentrations of intravenous anesthetics can be expressed for various endpoints such as movement, consciousness, recall, or hemodynamic responses. In this case, our interest was loss (and return) of consciousness.

The effect-site concentration of propofol required to obliterate consciousness is greater in the presence of pain or surgical stimulation (19). Our study in unstimulated volunteers thus best mimics the situation in patients being sedated for minimally stimulating procedures, or in whom surgical stimulation is blocked by regional anesthesia.

Factors that influence propofol requirement include age, lean body mass, central blood volume, hepatic blood flow, cardiac output, and hemorrhagic shock (20–24). For example, Schnider *et al.* (20) modeled age-related pharmacodynamic relationship between propofol plasma concentration and loss of consciousness and found that propofol plasma concentrations at loss of consciousness were 2.4 μg/mL in 25-year-old volunteers, 1.8 μg/mL in 50-year-old volunteers, and 1.2 μg/mL in 75-year-old volunteers. The estimated propofol effect-site concentration at loss of consciousness in our 26 ± 2 year old volunteers was 2.0 ± 0.9 μg/mL, which was similar to previous observations in which similar criteria for consciousness were used (6).

But even in our uniform group of young, healthy volunteers, the minimum estimated effect-site concentration that caused loss of consciousness was only a sixth of the highest required concentration. Some of this range no doubt results from inaccuracies in the Diprifusor kinetic model. But large differences in measured plasma concentrations at loss of consciousness have previously been reported (2,5,6). A consequence of this wide range in requirements is that it would be difficult or impossible to predict propofol requirement for individual patients based on average values for a given population. In other words, patients given a standard dose of propofol are likely to be inadequately or excessively sedated.

Our results indicate that propofol effect-site concentration at loss of consciousness is similar to that at awakening. The effect-site concentration at loss of consciousness can be used as guide

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to anesthetic management. An alternative to dosing propofol on the basis of average population requirements is thus to titrate propofol concentration to the concentration that obliterates consciousness in individual patients — and subsequently maintain a similar concentration. Naturally, the concentration could then be adjusted as necessary based on clinical needs. For example, the propofol concentration might be increased slightly during painful portions of a procedure. Nonetheless, our results suggest that so long as the propofol effect-site concentration does not much exceed the concentration initially required to produce lack of consciousness, patients can be expected to awaken quickly upon completion of the procedure and discontinuation of drug administration.

Although not tested in this study, it seems likely that this strategy will reduce the effect of elevated concentrations of propofol by giving patients concentrations that suit their individual needs. It is also likely that this strategy will apply to other sedatives and anesthetics.

In summary, there was a six-fold range in estimated propofol effect-site concentrations required to produce unconsciousness in a group of uniform volunteers. However, the average difference between individual effect-site concentrations at return and loss of consciousness was only 0.18 ± 0.17 μg/mL. Our results thus suggest an alternative to dosing propofol on the basis of average population requirements. Propofol can instead be titrated to the concentration that obliterates consciousness in individual patients, and subsequently maintained at a similar concentration. So long as the propofol effect-site concentration does not much exceed the concentration initially required to produce lack of consciousness, patients can be expected to awaken quickly upon completion of the procedure when drug administration is discontinued.

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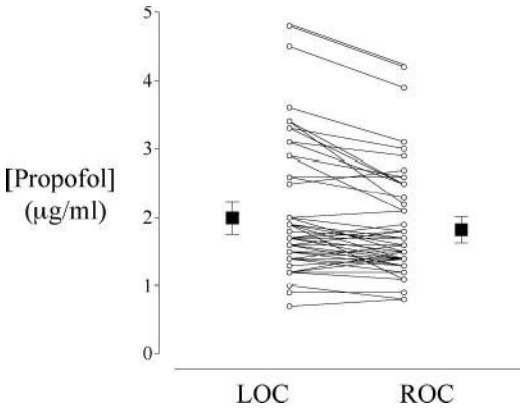

Fig. 1.

When the results from the three trials were combined, there was an excellent correlation between the effect-site concentration at loss of consciousness (LOC) and return of consciousness (ROC) in individual volunteers with ROC being slightly lower than LOC on average. Each response was elicited three times from each volunteer; thus on the graph, all three of the highest lines were from the same individual and all three of the lowest from another individual.