Analysis of Dose Escalation of Propofol Associated With Frequent Sedation

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Patients with dental phobia frequently require intravenous sedation to complete dental treatment. We encountered a case of a patient who received frequent sedation by propofol, which required escalation in the dosage of propofol required. The patient was a healthy young female with severe dental phobia, and the dental procedures were initiated under intravenous sedation. Intravenous sedation was administered to the patient more than 100 times over 9 years, and the dosages were analyzed. The mean dosage of propofol administered per hour was 6.9 ± 2.4 mg/kg/h, and the dosage tended to increase with frequency (0.06–0.1 mg/kg/h in each administration). Increased dosage was needed with a shorter interval between sedations after 30 episodes of sedation. Regarding the mean dosage of propofol per hour, the step-down method exhibited the highest increase in dosage rate of 0.18 mg/kg/h per administration followed by target-controlled infusion at 0.07 mg/kg/h per administration and combination sedation at 0.06 mg/kg/h per administration. We discuss factors that may be associated with acute tolerance to propofol when frequent propofol sedations are provided.

Key Words: Propofol; Dose escalation; Intravenous sedation; Dental phobia; Tolerance.

INTRODUCTION

Intravenous sedation is useful for performing dental procedures in patients with severe dental phobia.^{1,2} However, some patients with severe dental phobia tend to receive dental procedures under frequent intravenous sedation. We encountered a rare case of a patient with severe dental phobia who received intravenous sedation with propofol more than 100 times for various dental procedures. Here, we analyze the changes in dosage and frequency of propofol administration and also retrospectively examine the correlation between these factors.

CASE REPORT

The patient was a 24-year-old woman when she first visited our hospital in 2005. Her height was 156 cm, and

her body weight over the years varied from 40–42 kg. The patient had no notable medical history, except for one instance of hospitalization for 1 month because of acute pancreatitis at the age of 14 years.

At the age of 15 years, she experienced extreme pain and discomfort during forcible cavity excavation under insufficiently effective infiltration anesthesia, leading to the development of a severe dental phobia. Consequently, she refused any future dental treatments; therefore, her dental diseases remained untreated for a long period.

At the age of 24 years, she visited our hospital with a chief complaint of unbearable toothache. Of the 32 teeth present, she exhibited pathology of 17 teeth at initial consultation with panoramic radiograph. Dental pathology included caries, apical periodontitis, and cervical hypersensitivity, as well as generalized chronic periodontitis and pericoronitis. However, she refused to allow dental instruments near her mouth. When attempted, she developed acute hyperventilation and panic attacks. Therefore, consent was obtained for the necessary dental procedures to be completed under multiple intravenous sedations, with the primary medication being propofol.

Because of the expected numerous sedations, 2 different propofol infusion techniques were used: the

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target-controlled infusion (TCI) method and the step-down method. In the TCI method, the target blood concentration is achieved promptly and maintained automatically at a set target blood concentration based on the patient's age and weight in a preprogrammed TCI functionalized syringe pump. In the step-down method, the continuous administration rate of propofol, starting at 10 mg/kg/h (167 μ g/kg/min), is decreased manually in a stepwise fashion based on the patient's clinical sedative depth without using the TCI function.³ The sedative level in our university is initially targeted at level 3, as evaluated by the Ramsay sedation scale (appears asleep but arouses and responds to verbal command). However, if needed, deeper levels of sedation are provided, and this patient generally required at least a Ramsey 4 sedative level. Bispectral analysis or other electroencephalography monitoring for ambulatory sedation is not reimbursed with Japanese national health insurance, so this was not used.

ANALYSES OF SEDATION TREATMENTS

For this report, information on (a) the dental treatment, (b) the frequency and dosage of propofol administration, (c) the step-down method or the TCI method, (d) coadministered sedatives, (e) mean dosage of propofol (mg), (f) mean administration time of propofol (minutes), and (g) mean dosage of propofol per hour (mg/kg/h) was extracted by retrospective record review from all patient instances intravenous sedation based on previous sedation management charts, clinical records, and reports of remaining drugs. Thirteen dental anesthesiologists were eventually involved in the sedative management of this patient over 9 years.

We also performed regression analysis to examine the correlation between the mean dosage of propofol per hour (mg/kg/h) and the frequency of intravenous sedation with propofol. A level of statistical significance was set at a *p* value of <.05.

RESULTS

Intravenous sedation was administered to the patient up to 113 times over 9 years, resulting in a mean frequency of once per month. The dental treatments performed included endodontic treatment (78 times); scaling, irrigation, hyperesthesia treatment, and/or occlusal adjustments (14 times); restoration or prostheses adjustment (7 times); composite resin restorations (6 times); preparation of tooth and impression (6 times); and tooth extraction (2 times; Table 1). All of the above procedures were typical dental surgery or minor oral

surgery. Local anesthesia was used at the discretion of the dentist if significant surgical pain was expected.

The sedative of choice was propofol for intravenous sedation. Methods of propofol administration included TCI (89 times), step-down method (22 times), and a combination of both (2 times; Table 2). Propofol was administered alone 78 times, and propofol was combined with other drugs 35 times.

The drugs used for combination sedation included midazolam (21 times), butorphanol (5 times), midazolam and butorphanol (5 times), and fentanyl (4 times; Table 3).

The mean dosage of propofol for all sedations was 303 ± 217 mg, and the mean administration time was 64 ± 34 minutes. Therefore, the mean dosage of propofol administered was 6.9 ± 2.4 mg/kg/h (115 ± 40 μ g/kg/min; Table 4).

The correlation between the frequency of intravenous sedation and mean dosage of propofol is shown in Figure 1. The dosage tended to increase with frequency, particularly after the 30th episode of intravenous sedation (Figure 1). In addition, as the administration interval decreased, a tendency for a considerable increase in propofol dosage was observed (Figure 1). Conversely, a tendency for a lesser increase in propofol dosage was seen when other drugs were combined, such as midazolam (Figure 2).

The step-down method exhibited the highest increase in mean propofol dosage rate of 0.18 mg/kg/h per administration, followed by TCI at 0.07 mg/kg/h per administration, and then combination sedation at 0.06 mg/kg/h per administration (Figures 2 and 3). A significant positive correlation was observed between the frequency of intravenous sedation and the increased dosage of propofol required.

DISCUSSION

Frequently, when dental care under sedation or general anesthesia is needed for adult patients, all dental treatment can be completed in a few visits or even in one visit if significant pathology is not present. This patient required many more treatment sessions than is typical. We believe that the high frequency of intravenous sedations for this patient occurred mainly because she required frequent endodontic treatments of a short duration. Although in many patients, multiple complete endodontic treatments can be done at one time, this patient commonly experienced hyperesthesia and pain after endodontic treatment. Therefore, 2 to 3 appointments were needed for endodontic treatment of each tooth. She eventually even needed multiple endodontic retreatments because she complained of occlusal pain

Table 1. Dental Procedures Performed

<i>Dental Procedure</i>	<i>Number of Times</i>
Endodontic treatment	78
Scaling/irrigation/hyperesthesia treatment/occlusal Adjustments	14
Temporary crown/crown/inlay set	7
Composite resin restorations	6
Preparation of tooth/impression	6
Tooth extraction	2

from the provisional restorations, despite what appeared to be clinically adequate root canal treatments and significant occlusal adjustments.

Under moderate sedation (Ramsey level 3), the patient refused us even touching her mouth. Therefore, the appropriate sedative level was always achieved when the patient's refusal response disappeared, and this appropriate sedative level was always around level 4 on the Ramsay sedation scale (asleep, brisk response to light, glabella tap, or loud noise). Consequently, the depth of sedation for each dental procedure was determined based on the patient's acceptance of treatment rather than the dental anesthesiologist's arbitrary decision of the appropriate dose of propofol. It is likely that the difference in sedative level achieved by each dental anesthesiologist was relatively small, but it was a clinically determined value and therefore subject to interpretation. Moreover, some dental anesthesiologists noticed that the consumption of propofol was increasing during sedations after relatively stable doses early on in the treatment sessions. Thereafter, some dental anesthesiologists tried various methods and drug combinations to avoid the dose escalation of propofol. However, a rapid increase in the dose of propofol was not recognized during the early sessions of intravenous sedation.

The dose escalation of propofol could be due to either pharmacokinetic effects, such as alterations in drug metabolism through repeated exposure or extrahepatic metabolism, or pharmacodynamic effects, such as receptor adaptation. Moreover, there are case reports of multiple propofol sedations for children undergoing frequent procedures.^{4,5} These studies also showed an increase in propofol dosage, and it was speculated that the mechanisms of tolerance might be attributed to

Table 2. Administration Method for Propofol Sedation

<i>Method</i>	<i>Number of Times</i>
Target-controlled infusion (TCI)	89
Step-down method	22
TCI + step-down method	2

Table 3. Combination Drugs Used

<i>Drugs</i>	<i>Number of Times</i>
Midazolam	21
Butorphanol	5
Midazolam + butorphanol	5
Fentanyl	4

altered physical status of neuronal membranes or to alterations in neurotransmitter levels of receptors.^{4,5}

In our case, the mean dosage of propofol administered per hour tended to increase most with decreasing administration interval. Conversely, if the administration interval of propofol increased, the mean dosage administered per hour tended to decrease. This suggests to us what appeared to be tolerance toward propofol induced by short intervals of administration that could be reversed by increased propofol-free intervals. Hence, we believe that the short intervals of propofol administration after both the 30th sedation and after the 63rd sedation contributed to a considerable increase in observed dosage. In studies by Ihmsen et al^{6,7} involving examination of acute tolerance in rats, the authors reported that the maintenance dosage of propofol increased by 0.6 mg/kg/min. This was in accordance with our results. They suggested that metabolic tolerance developed, although it was difficult to draw definite conclusions regarding the same.^{6,7}

Our results confirm that the combined use of other sedatives, such as midazolam, can reduce the required dose of propofol, but it is possible that additional sedatives also inhibited the development of acute tolerance to propofol. Hsieh et al⁸ also reported that the dosage of propofol decreased upon combination with meperidine compared with propofol administration alone. In addition, it has also been reported that synergy up to 1.44 times was observed when midazolam was combined with propofol.⁹ However, Taylor et al¹⁰ reported that there were no significant differences in total propofol dosages or recovery times between administration of propofol alone and administration of propofol in combination with 2 mg midazolam. In the Japanese health insurance system, the use of mu agonist

Table 4. Features of All Sedation Episodes

<i>Total number of sedations</i>	<i>113</i>
Time period	9 years
Mean number of sedations per month	1.0
Mean total dosage of propofol	303 ± 217 mg
Mean total administration time	64 ± 34 min
Mean infusion dosage of propofol	6.9 ± 2.4 mg/kg/h
Propofol combined with other drugs	35/113 times

Figure 1. Changes in mean infusion rate of propofol. Graphs show the correlation between the frequency of intravenous sedation and mean dosage of propofol. In the upper graph, the dosage tended to increase with increasing frequency, particularly after the 30th and the 60th episode of intravenous sedation. In the lower graph, as the administration interval decreased, a tendency of a considerable increase in propofol dosage was observed.

Figure 2. Regression and correlation analysis between the mean infusion rate of propofol and frequency (total number of cases, only propofol, propofol, and other sedative drugs). A significant positive correlation was observed between the frequency of intravenous sedation and the dosage of propofol. A tendency for a slower increase in propofol dosage was seen when combined with other drugs such as midazolam $\pm$ butorphanol, as the slope of the regression line is decreased.

opioids for ambulatory intravenous sedation is generally not reimbursed. Therefore, midazolam and the agonist-antagonist analgesic, butorphanol, were mainly used as the combination drugs. It is known that less propofol is needed to reach the same level of sedation when

adequate doses of opioids or other sedatives are combined with propofol.

In our case, however, it appeared that as the frequency of sedations increased, so did the required infusion dose of propofol. This could be lessened by the

Figure 3. Regression and correlation analysis between the mean infusion rate of propofol and frequency (total number of cases, target-controlled infusion, and step-down method). A significant positive correlation was observed between the frequency of intravenous sedation and the dosage of propofol in each situation. The step-down method exhibited the higher increase in rate of propofol infusion at 0.18 mg/kg/h per administration versus TCI at 0.07 mg/kg/h per administration.

addition of concomitant sedative or analgesic drugs. Most of the other sedatives that were combined with propofol were administered as a bolus at the start of intravenous propofol sedation. This will generally allow appropriate levels of sedation to be achieved rapidly with lower blood concentrations of propofol, resulting in a decrease in the overall mean dosage of propofol. We speculate, however, that it is the rapid achievement of appropriate sedative levels that plays a part in the inhibition of the mean dosage of propofol by helping to inhibit the development of acute tolerance to propofol. Although not specifically studied, if lower propofol infusion rates were needed later during a given sedation, when the effect of other sedatives or opioids had dissipated, this would confirm that achieving an appropriate sedative level rapidly may also help prevent the development of acute tolerance. Differences in charting infusion dosages prevented us from studying this parameter.

We also found an increase in overall propofol dosage in the step-down method versus in the TCI method. Matsumoto et al¹¹ also reported that propofol dosage significantly decreased in the TCI method compared with the step-down method for sedation during gynecological operations. They speculated that this occurs because the blood concentration of propofol increases more rapidly in the TCI method than in the step-down method. This is consistent with our assumption that achieving a rapid sedative level helps prevent acute propofol tolerance.

Although we suspect that acute tolerance was the reason for the increased dosage of propofol necessary to achieve adequate sedation during frequent appointments for this patient, other possibilities should be considered. It may be that the consumption of propofol increased due to an increase in the patient's state anxiety. It is also possible that this patient may have, unknown to us, been using alcohol, or even illicit drugs, on a regular basis to account for her increased dosage of propofol. We did question the patient regarding drug abuse/addiction, including alcohol, or personal problems, but they were denied or the patient withheld this information from us. Regardless, it appeared that the greatest increased dosage of propofol required for adequate sedation was during the most frequent visits, which led us to conclude that this was a case of acute tolerance.

CONCLUSION

The use of propofol for more than 100 sedations based on titration to clinical endpoints, and using multiple anesthesiologists, yielded the following results:

- The dosage increased, on average, 0.06–0.1 mg/kg/h during each administration.
- Tolerance to propofol appeared to develop after 30 and 63 episodes of sedation associated with shorter intervals between sedations.
- Acute tolerance to propofol may be inhibited when sedative levels are rapidly achieved, such as with TCIs or when other sedatives or opioids are coadministered.

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