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Amnesia for electric dental pulp stimulation and picture recall test under different levels of propofol or midazolam sedation

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Abstract

Purpose: The aim of this study was to compare the amnesic effect of propofol and midazolam to an electric (invasive) dental pulp stimulation and picture recall (noninvasive) test at two sedation levels with the aid of the bispectral index (BIS) monitoring.

Method: The subjects were 10 male volunteers (24-34 years) classified in the ASA physical status I. Propofol was administered to achieve sedation score 3 with a target controlled infusion (TCI) technique, and then it was regulated at sedation score 2 (P group). Midazolam was administered by a titration dosage to achieve sedation score 3 (M group). BIS score, sedation score, plasma/serum concentration of propofol and midazolam, blood pressure, pulse rate, respiratory rate, end-tidal CO₂ tension, and arterial oxygen saturation were observed. Amnesic effects were evaluated using picture recall test and electric dental pulp stimulation at each sedation level in both groups.

Result: No difference was observed in amnesic effects evaluated by picture recall test at two sedation levels. Likewise, there was no difference at sedation score 3 when evaluated by electric dental pulp stimulation. In contrast, significant difference was observed at sedation score 2; midazolam produced amnesia in more subjects than propofol.

Conclusion: Propofol and midazolam did not show any significant difference in amnesic effects to noninvasive stimuli. In invasive stimuli, midazolam showed stronger amnesic effect in the moderate, but not at the deeper sedation level.

Keywords: amnesia, propofol, midazolam, intravenous sedation, bispectral index
Introduction

A number of unpleasant and painful procedures may be given to the patients in dentistry (1). Fear and anxiety related to past experiences can lead to medical emergencies such as hyperventilation syndrome, vasodepressor syncope, and cardiovascular accidents. To prevent these complications and to produce a beneficial amnesia, intravenous sedation is widely used (2,3).

Midazolam, a benzodiazepine derivative, is a well-known good sedative with quick onset and a short half-life. Propofol is also rapidly redistributed and metabolized, though it causes some venous irritation. Since propofol is easily titratable, it becomes more common for intravenous sedation.

Roode et al. (4) administered either propofol or midazolam to subjects and compared their ability to recall. No significant difference in memory recall was found between two drugs. In contrast, in another study examining amnesic effect of propofol using an injection needle as a painful stimulation (5), it was reported that amnesia occurred in only 50% of the subjects. Since midazolam is well recognized to have profound amnesic effects (6-8), the magnitude of amnesic effects may be a major difference between two sedative agents.

In this study, therefore, we administered propofol and midazolam to subjects to produce the same sedation level with the aid of the bispectral index (BIS) monitoring and compared amnesic effect at two different sedation levels using an electric (invasive) dental pulp stimulation and picture recall (noninvasive) test. BIS monitoring is known to be a suitable indicator of sedation level (9-13), and many studies suggest a correlation between the BIS value and amnesia (14,15)

Methods

Ten healthy adult male volunteers participated in this study. Their age was 28.8±4.1 (24-34) years and body weight was 65.5±12.0 (52-88) kg. We obtained informed consent from all subjects. This study was approved by the ethical committee, Tokyo Dental College. Each subject received three experiments in at least one-week interval in a randomized crossover manner. At each experiment, the subjects received propofol (P group), midazolam (M group) or no medication (C group). Venous line was established with a 22G cannula in the left cephalic vein of the subjects in a supine position. Another cannula was inserted in the right cephalic vein for blood sampling.

In the P group, propofol (Diprivan®, Astra Zeneca Japan, Kita-ku, Osaka, Japan) was infused using Terufusion TCI pump TE-371 (Terumo Corporation,
Shibuya-ku, Tokyo, Japan) with an default plasma concentration of 1.5 μg·l⁻¹. Sedation level was maintained at score 3 (16) for ten minutes. Then the infusion rate was decreased and maintained to achieve score 2 for ten minutes. Thereafter, the infusion was stopped. In the M group, midazolam (Dormicum®, Yamanouchi Pharma, Chuo-ku, Tokyo, Japan) was titrated to achieve score 3. After midazolam injection, sedation level of the subjects gradually decreased to score 2. In the C group, observation was made in a similar fashion for 30 minutes under no medication.

Observations were made before drug administration (control), when the sedation scores reached 3 and 2, and when the subjects were evaluated to be completely recovered. In the C group, observations were made every five minutes after hemodynamic stability was established. Observations included sedation score, BIS score, indirect blood pressure (BP), pulse rate (PR), respiratory rate (RR), endtidal CO₂ tension (ETCO₂), and arterial oxygen saturation (SpO₂). Amnesic effects were evaluated using picture recall test followed by electric dental pulp stimulation. Venous blood was sampled when the sedation score reached 3 and 2 and when subjects completely recovered to analyze plasma propofol or serum midazolam concentration. Blood sampling was performed after each evaluation of amnesic effect. Table 1 shows sedation scores (16). One of the authors assessed all sedation scores. A sensor (BIS plus®) of a BIS monitor (Ver. 2.21, A-2000, ASPECT, Nihon Kohden, Shibuya-ku, Tokyo, Japan) was placed on the forehead of the subjects. BIS score was continuously monitored throughout the study. BP, PR and SpO₂ were monitored with automated monitoring equipment (Moneo BP-8®8, Nippon Collin, Bunkyo-ku, Tokyo, Japan). RR and ETCO₂ were monitored with a respiratory monitor (CAPNOMAC ULTIMA®, Datex Ohmeda, Hino-shi, Tokyo, Japan). A sampling tube was inserted and fixed in the subject’s left nostril.

When the sedation score reached 3 and 2 as well as when recovery was ensured, subjects were presented with three different pictures and asked to memorize them for picture recall test. We used different pictures for each group. The pictures were images of animals, vehicles, and tools printed on 10 x 10cm cards. These cards were shown to the subjects in each experiments in randomized manner. These cards included one of animal cards, one of vehicle card, and one of tool card. For electric dental pulp stimulation, we used a pulp tester (Sirotest II®) manufactured by SIEMENS Corporation Japan (Shibuya-ku, Tokyo, Japan). The target teeth were three vital lateral incisors in either the maxilla or the mandible. Different tooth was stimulated at each time when the sedation score reached 3 and 2 and when subjects recovered. For each tooth, the stimulation was given immediately after the picture recall test. Electric
current was increased until pain perception occurred. We evaluated the amnesic effect 30 minutes after complete recovery from sedation was established. This included clear consciousness, no sleepiness and no staggering. The subjects were asked to describe the picture image and the region on which electrical stimulation was given. If the subject had amnesia to both tests, the score was 2. If he remembered one, but not the other, the score was 1. If he recalled both, the score was 0.

Predicted plasma and effect site concentrations of propofol were calculated by a TCI pump. Plasma propofol concentration was analyzed using a high performance liquid chromatography with a fluorescence detector. Using a pharmacokinetic analysis software (Palmacokinetics Ver. 0.53) on the Palm® operating system (Palm Japan, Tokyo, Japan), predicted serum and effect site concentrations of midazolam were calculated. Serum midazolam concentration was analyzed using a gas chromatography with a nitrogen-selective detector.

Data are shown as the mean ± standard deviation. Repeated Measures ANOVA and Friedman's $\chi^2$ r-test were applied where appropriate. For multiple comparisons, Dunnett's test was used. Spearman's rank correlation coefficient was used to analyze the relationship of sedation score, BIS score, amnesic score, and plasma/serum drug concentrations. A P value less than 5% was considered to be significant.

Results

The sedation score 3 was attained 222.0 ± 62.0 sec and 168.0 ± 40.5 sec after the start of propofol infusion and midazolam injection, respectively. There were no significant differences between two groups. The sedation score reached 2 and 0 24.0 ± 7.0 and 44.5 ± 8.0 min after the start of propofol infusion and 34.5 ± 7.3 and 64.0 ± 10.5 min after midazolam injection, respectively.

When the sedation score was 3, BIS score was 73.7 ± 9.1 in the P group and 76.1 ± 5.4 in the M group, respectively. Although these scores were lower than that in the C group, there was no difference between two BIS scores. When the sedation score was 2, the former was 85.3 ± 4.7 and the latter was 82.5 ± 6.5. There were no differences in BIS scores among three groups. The BIS score in the C group was lower compared to those in the P and M groups after recovery (Table 2). The correlation between sedation and BIS scores was quite high: $r=0.86$ in the P group and $r=0.77$ in the M group (Fig.1).

In the P group, diastolic BP decreased for 35 minutes compared to the control value. In the M group, systolic and diastolic BPs did not change from the control value.
There were no differences in PR among groups. There were also no differences both within each group and among groups in RR, ETCO₂, and SpO₂.

When the sedation score was 3, the picture recall test revealed that eight subjects in the P group and all subjects in the M group had amnesia, while electric dental pulp stimulation indicated that nine subjects in the P group and all subjects in the M group had amnesia. When the sedation score was 2, the picture recall test revealed that seven subjects in the P group and five subjects in the M group had amnesia, while electric dental pulp stimulation indicated that two subjects in the P group and eight subjects in the M group had amnesia. For picture recall test, there was no significant difference between two drugs and between the results obtained with sedation scores of 3 or 2. For electric dental pulp stimulation, although there was no significant difference between the groups when the sedation score was 3, midazolam showed a significantly higher amnesic effect when sedation score was 2. The correlation between BIS score and amnesic effect was quite high: r=0.82 in the P group and r=0.83 in the M group, respectively. The correlation between sedation score and amnesic effect was r=0.81 in the P group and r=0.89 in the M group, respectively.

The measured plasma propofol concentration when the sedation scores were 3, 2 and 0 were 1.5 ± 0.6 μg·ml⁻¹, 0.5 ± 0.2 μg·ml⁻¹, and 0.2 ± 0.1 μg·ml⁻¹, respectively (Table 3). There were no differences between measured and predicted propofol concentrations. The correlation coefficients between plasma propofol concentration and BIS score, sedation score and amnesic effect were r=0.70, r=0.92 and r=0.64, respectively. Average dosage of midazolam per body weight was 0.04±0.01 mg·kg⁻¹. The measured serum midazolam concentrations when the sedation scores were 3, 2 and 0 were 60.7±11.7 ng·ml⁻¹, 28.5±9.3 ng·ml⁻¹, and 20.0±7.4 ng·ml⁻¹, respectively (Table 3). There were also no differences between measured and the predicted midazolam concentrations. The correlation coefficients between serum midazolam concentration and BIS score, sedation score and amnesic effect were r=0.71, r=0.82 and r=0.62, respectively.

Discussion

Both propofol and midazolam showed similar amnesic effect for picture recall test. In contrast, when using an invasive electric dental pulp stimulation, midazolam produced amnesia in more subjects in the moderate, but not at the deeper sedation level. In addition, BIS scores were found to have good correlations to both sedation score and amnesic effect.

In this study, sedation level of the subjects was classified by a score defined
by Kaneko(16). In this score, stages 2 and 3 of the Ramsey Scale(17) were further divided into four substages. The level of intravenous sedation level could be approximately adjusted for respective dental procedures using this score in our routine practices.

We used an infusion pump for propofol infusion using a TCI technique. Since the half-life of propofol is shorter and titration is easier than midazolam, it is easy to maintain steady sedation level with propofol infusion. Midazolam, despite relatively short half-life among benzodiazepines, is more difficult to adjust sedation level than propofol. Midazolam has an elimination half-life between 1.5 and 5 hours, and a single dose of 0.05 - 0.075 mg·kg⁻¹ can give a sedative effect lasting 20 to 60 minutes. It takes 75 to 120 minutes to recover (7). In addition, sedative effect of midazolam decreases as time elapses. Therefore, infusion rate of propofol was stepwisely decreased (every 10 minutes) to obtain similar sedation level with that in the M group.

A number of methods have been used to evaluate amnesia. Noninvasive methods include pictures recall(11), as well as language recall (4,11,14,15). Invasive methods, on the other hand, include surgical procedures and other treatments (18-21). Veselis et al. (22) administered propofol, midazolam, thiopental and fentanyl via a TCI technique to volunteers and compared sedation level and amnesic effect using verbal and visual tasks. They concluded that in subjects with equal sedation scores, propofol and midazolam have similar effects on amnesia.

We used a pulp tester for electric dental pulp stimulation, which is normally used to assess the health status of dental pulp, as an invasive stimulus. There have been no previous studies that used electric dental pulp stimulation to examine amnesic effects. Although picture recall test did not show any significant difference in amnesia between two agents, electric dental pulp stimulation showed a significant difference at sedation score 2 in this study. This result may indicate that midazolam causes amnesia when sedation is moderate even if it does not eliminate the pain perception of pain. In contrast, propofol may be less useful in depressing the perception to painful stimuli and in producing amnesic effect if the sedation level is moderate. According to Liu et al. (14,23) and Chernik et al. (24), the BIS score and sedation level are highly correlated and may also be related with amnesic effect. Our study also identified correlations among BIS score, sedation level and amnesic effect. Nonetheless, even when the BIS scores are the same, propofol resulted in weak amnesic effects for invasive stimulation in moderate sedation level. Therefore, we should take this fact into consideration during propofol sedation. In addition, when the sedation score was 2, there was no difference in BIS scores among the three groups. Furthermore, when recovery was confirmed in P
and M groups, the C group showed lower BIS scores. It is suggested that the subjects in the C group closed their eyes and might become drowsy over time (25, 26).

Since the electric current might pass through the electrode during electric dental pulp stimulation, it was possible that the BIS scores might be affected. However, no such effects were observed during experiment. We believe this was because the current for electric dental pulp stimulation is significantly weaker than that used for the electric cauterization or similar devices. The electric pulp tester that we used in this study was small, wireless, with a step-wise assessment function making it convenient for use at the chair-side situation. Because neither incision nor needles are required, the device appears to be useful as an invasive stimulus for the evaluation of amnesia. Although the electric pulp tester assessed pain thresholds in a step-wise manner, a tester displaying values of electric current might have enabled more detailed examination. Since we randomly examined maxillary and mandible incisors in this study, differences enamel thickness and pulp volume might to some extent affect the responses to the electric pulp tests.

This study shows no significant differences between predicted values and measured values. Furthermore, there was a correlation between plasma/serum concentrations and amnesic effects. Nonetheless, when the amnesia score was 2, plasma/serum concentrations varied among individuals, ranging from 0.2 to 2.3 $\mu$g·ml$^{-1}$ for propofol and from 19 to 74 ng·ml$^{-1}$ for midazolam. It is therefore suggested that taking individual differences into consideration is important in clinical settings. Measured serum midazolam concentration at recovery was 20.0±7.4 ng·ml$^{-1}$. Since this value was about 1/3 of that at sedation score 3, it was possible that the subjects might be still lightly sedated and their recall might be to some extent affected. However, predicted effect site concentration of midazolam was less than 1/5 of that at sedation score 3. This was also less than the ratio of effect site concentration at recovery and sedation score 3 of propofol. Therefore, we believe that the effect of residual midazolam on amnesic effect at recovery was minimal.

Because only male subjects participated in this study, any sex difference is unknown. It is commonly stated that women have higher pain thresholds than men. In addition, this study was conducted on healthy volunteers. However, patients would have largely different preoperational anxiety. Thus, it will be necessary to identify the level of anxiety that may affect the level of sedation or amnesia.

In conclusion, propofol and midazolam did not show any significant difference in amnesic effects to noninvasive stimuli. For invasive stimuli, there is no significant difference while under deep sedation, but midazolam caused more amnesia.
under moderate sedation. Further study is needed to evaluate if this can be used for optimizing individual sedation.
References

### Table 1  
**sedation score**

<table>
<thead>
<tr>
<th>level</th>
<th>Subjective symptoms</th>
<th>Objective symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 light</td>
<td>feeling of ease</td>
<td>talkativeness, quick response</td>
</tr>
<tr>
<td>2 moderate</td>
<td>no anxiety</td>
<td>mild relaxation, mild slurring, slow response, mild blepharoptosis</td>
</tr>
<tr>
<td></td>
<td>strong relaxation</td>
<td></td>
</tr>
<tr>
<td></td>
<td>comfortable feeling</td>
<td></td>
</tr>
<tr>
<td>3 deep</td>
<td>strong sleepiness</td>
<td>relaxation, slurred speech</td>
</tr>
<tr>
<td></td>
<td>comfortable feeling</td>
<td>slow response or no response</td>
</tr>
<tr>
<td></td>
<td>indiffereness</td>
<td>blepharoptosis</td>
</tr>
<tr>
<td>4 asleep</td>
<td>none</td>
<td>no response</td>
</tr>
</tbody>
</table>

(From Y. Kaneko, Masui 1998; 47(suppl): S52-S60)

### Table 2
When the sedation score was three, these scores were lower than that in the C group, there was no difference in two BIS scores.

When the sedation score was two, there were no differences in BIS scores among all three groups.

The BIS score in the C group was lower compared to those in the P and M groups after recovery.

<table>
<thead>
<tr>
<th>Control value</th>
<th>Sedation score</th>
<th>recovery</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Control</td>
<td>95.0(2.7)</td>
<td>92.4(6.4)</td>
</tr>
<tr>
<td>Propofol</td>
<td>96.2(1.7)</td>
<td>73.7(9.1)</td>
</tr>
<tr>
<td>Midazolam</td>
<td>96.8(1.0)</td>
<td>76.1(5.4)</td>
</tr>
</tbody>
</table>

Mean(S.D)
Fig. 1 Relationship between sedation scale and BIS score
The correlation between sedation and BIS scores was quite high:
r=0.86 in the P group and r=0.77 in the M group.

Table 3  Plasma/Serum concentration

<table>
<thead>
<tr>
<th></th>
<th>Sedation score</th>
<th>recovery</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td><strong>Propofol (μg/ml)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Predicted plasma concentration</td>
<td>1.4(0.4)</td>
<td>0.5(0.2)</td>
</tr>
<tr>
<td>Effect site concentration</td>
<td>1.4(0.3)</td>
<td>0.6(0.2)</td>
</tr>
<tr>
<td>Plasma concentration</td>
<td>1.4(0.6)</td>
<td>0.5(0.2)</td>
</tr>
<tr>
<td><strong>Midazolam (ng/ml)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Predicted serum concentration</td>
<td>56.9(13.4)</td>
<td>21.7(9.8)</td>
</tr>
<tr>
<td>Effect site concentration</td>
<td>43.2(19.1)</td>
<td>13.5(7.2)</td>
</tr>
<tr>
<td>Serum concentration</td>
<td>60.7(11.3)</td>
<td>28.5(9.2)</td>
</tr>
</tbody>
</table>

Mean(S.D)