Effect of remifentanil on plasma propofol concentration and bispectral index during propofol anaesthesia

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Editor’s key points
- Remifentanil during propofol TCI decreased heart rate, arterial pressure, and cardiac index.
- A decrease in indocyanine green disappearance ratio accompanied an increase in plasma propofol.
- This suggests a decrease in hepatic clearance of propofol.
- The increased plasma propofol had no suppressive effect on BIS.

Background. Propofol and remifentanil are commonly administered together in clinical anaesthesia, but the effect of remifentanil on the plasma concentration of propofol has yet to be established. The aim of the present study was to investigate the effect of remifentanil on plasma propofol concentrations (Cp) in the absence of surgical stimulation.

Methods. Thirty-eight patients undergoing elective gynaecologic surgery were randomly assigned to receive one of the three remifentanil doses (0, 0.5, or 1.0 μg kg⁻¹ min⁻¹). Anaesthesia was induced by a target-controlled infusion of propofol. After tracheal intubation, saline or remifentanil infusion was administered for 15 min. Mean arterial pressure (MAP), heart rate (HR), and bispectral index (BIS) were recorded and cardiac index (CI), blood volume, and indocyanine green disappearance ratio (K-ICG) were measured using a dye densitogram analyser before and 15 min after saline or remifentanil infusion. Cp was measured using high-performance liquid chromatography.

Results. HR, K-ICG, and BIS were significantly decreased in the remifentanil 0 μg kg⁻¹ min⁻¹ group. The decrease in MAP, HR, CI, and K-ICG was significantly lower in the remifentanil 0.5 and 1.0 μg kg⁻¹ min⁻¹ groups compared with the remifentanil 0 μg kg⁻¹ min⁻¹ group. Cp was significantly increased after remifentanil administration, but this had no influence on BIS.

Conclusions. Remifentanil reduced the CI and increased the Cp, which may be related to a decrease in the K-ICG, but had no significant effect on the BIS.

Keywords: anaesthetics i.v., propofol; analgesics opioid, remifentanil; blood, anaesthetic concentration; monitoring, bispectral index

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Remifentanil is a short-acting opioid that is widely used during general anaesthesia. Remifentanil reduces the haemodynamic and bispectral index (BIS) response to tracheal intubation and the haemodynamic response to skin incision. Remifentanil is coadministered with propofol in the clinical setting. Propofol and remifentanil interact pharmacodynamically and act synergistically in response surface models of hypnosis and nociception.

Because propofol is a high clearance drug, the plasma propofol concentration (Cp) is influenced by cardiac output (CO). During constant infusion of propofol, catecholamines decrease the Cp in ovine and propranolol increases the Cp in swine. In humans, dopamine increases CO with a significant decrease in the Cp during propofol anaesthesia. Sevoflurane increases the Cp, which is accompanied by a decrease in CO. It is not known, however, whether remifentanil increases the Cp during propofol anaesthesia. Because remifentanil suppresses the heart rate (HR), arterial pressure, and CO, remifentanil may decrease the blood flow at propofol clearance sites and increase the Cp during constant propofol infusion.

The bispectral index (BIS), derived for the EEG, is used to estimate cerebral drug effect and decreases monotonically with an increase in Cp during propofol anaesthesia. If coadministration of remifentanil increases the Cp during propofol anaesthesia, remifentanil may suppress BIS. In fact, it was previously reported that remifentanil decreases BIS during general anaesthesia. Therefore, in the present study, we investigated the effect of remifentanil on the Cp and BIS during propofol anaesthesia in patients without surgical stimulation. We hypothesized that remifentanil reduces CO and liver blood flow, and increases the Cp, leading to a significant decrease in the Cp during propofol anaesthesia.

Methods

The study was approved by the Ethics Committee of the National Defense Medical College (Saitama, Japan), and informed consent was obtained from 38 female patients (ASA physical status I–II, 20–69 yr of age) undergoing elective gynaecologic surgery. Exclusion criteria included disease
or injury affecting the central nervous system, recent use of psychoactive or analgesic medication, neurologic disorders, thyroid disease, allergy to iodine, alcohol or drug abuse, and weight <70% or more than 130% of ideal body weight. To avoid awareness during the study period, patients were excluded if the BIS was higher than 65 before tracheal intubation.

Premedication was not given before inducing general anaesthesia. Patients were randomly assigned to one of the three remifentanil dose groups (0, 0.5, or 1.0 µg kg⁻¹ min⁻¹). After arrival in the operating theatre, arterial pressure, electrocardiography, and pulse oximetry were monitored using a Datex-Ohmeda S/5 anaesthesia monitor system (GE Healthcare, Helsinki, Finland) and 500 ml of 6% hydroxyethyl starch 70000 (HESPANDER Injection, Fresenius Kabi Japan, Tokyo, Japan) was infused, followed by 80 ml h⁻¹ of acetated Ringer’s solution in all patients. An epidural catheter was inserted in all patients, but no drugs were injected epidurally until completion of the study period. Before anaesthesia induction, i.v. lidocaine (20 mg) was administered to block stimuli induced by the drug injection. Anaesthesia was induced by propofol target-controlled infusion (TCI; a target plasma concentration of 6 µg ml⁻¹) using a Diprifusor TCI pump (Terumo Corporation, Tokyo, Japan) based on the kinetic studies of Marsh and colleagues. Propofol was administered directly via an i.v. catheter to prevent propofol concentration instability due to the length of the i.v. extension line or the background infusion rate. Ninety seconds after anaesthesia induction, the target concentration of propofol was reduced to 4 µg ml⁻¹, and rocuronium (1.0 mg kg⁻¹) was administered after the loss of a response to verbal commands. A cannula was placed in the radial artery after local anaesthesia with 1% lidocaine for invasive arterial pressure monitoring and blood sampling. Five minutes after anaesthesia induction, tracheal intubation was performed. In all patients, 8% lidocaine was sprayed on the larynx and 1 ml of 4% lidocaine was injected into the trachea using an intra-tracheal spray tube (10 Fr, 160 mm, R 100, Hakko-Medical, Tokyo, Japan) before tracheal intubation. After tracheal intubation, ventilation was controlled to maintain end-tidal CO₂ at 35–40 mm Hg with a fresh gas flow of 6 litre min⁻¹ (45% oxygen). Tympanic temperature was continuously monitored using an earphone-type infrared tympanic thermometer and maintained within 0.5°C during the study period. To obtain dye densitograms (DDG-3300, Nihon Kohden, Tokyo, Japan), a probe with two light-emitting diode infrared sources (wavelengths of 805 and 940 nm) was attached to a nostril. After a 15 min maintenance period (15 min after tracheal intubation), saline or remifentanil (0.5 or 1.0 µg kg⁻¹ min⁻¹) infusion was initiated for 15 min. All drugs were diluted to a comparable volume with saline, and drug concentrations were adjusted to give a similar infusion rate. The investigators were blinded to the drug preparations. Before and 15 min after study drug infusion, mean arterial pressure (MAP), HR, BIS, suppression ratio (SR) on the BIS monitor, cardiac index (CI), blood volume (BV), and indocyanine green (ICG) disappearance rate (K-ICG) were recorded, and single blood sampling was performed at the same time. The BIS was monitored with a BIS XP Monitor (ver. 3.4) with a Quatro sensor (Aspect Medical Systems, Newton, MA, USA). The smoothening time was set at 15 s. CI, BV, and K-ICG were measured by injection of 10 mg ICG (Diagno-green, Dai-ichi Pharmaceutical, Tokyo, Japan) followed by a saline flush (20 ml). Blood samples were separated and plasma samples were stored at −20°C until extraction and assay. Arterial pressure, HR, BIS, and SR were captured online every 4 s and downloaded using an automated anaesthesia recording system (ERGA ver. 4, SEIRYO Computer Inc., Shizuoka, Japan). The downloaded data for 1 min before and at 15 min after study drug infusion were averaged and used for statistical analysis.

Total plasma Cp was measured as reported previously using high-performance liquid chromatography. The chromatography apparatus consisted of a dual-head pump with an autoinjector (SIL-10AD; Shimadzu, Kyoto, Japan) serially connected to a spectrofluorometric detector (RF-550; Shimadzu). The spectrofluorometric detector was set with an excitation wavelength of 276 nm, an emission wavelength of 310 nm, and 15 nm slit widths. To each 400 µl sample, 1.0 ml of a precipitating solution (acetonitrile) containing 1 µg thymol (internal standard) was added, and the sample was then mixed with a vortex mixer for 30 s. The mixed samples were injected into a 25 cm × 4.6 mm ID Inertsil ODS-3 high-performance liquid chromatography column (GL Science, Tokyo, Japan). The detection limit of this apparatus is 10 ng ml⁻¹, and we confirmed the linearity of the signal concentration ratio from 50 ng ml⁻¹ to 10 µg ml⁻¹ before measurement (r²=0.9998).

A sample size calculation estimated that an increase in Cp of 0.5 µg ml⁻¹ with a standard deviation of 0.3 µg ml⁻¹ would require 12 subjects with a power of 0.95 and an α of 0.05. Differences in age, weight, and height between the groups were analysed with the Kruskal–Wallis test. Changes in MAP, HR, BIS, SR, CI, BV, K-ICG, and Cp within the groups (pre-infusion vs 15 min after drug infusion) were compared using the Wilcoxon test. Comparisons of the effect of remifentanil on MAP, HR, BIS, SR, CI, BV, K-ICG, and Cp between the groups were performed using a two-way ANOVA followed by Bonferroni’s correction for multiple comparisons test. ΔCI, ΔK-ICG, and ΔCp (difference between the values before infusion and 15 min after drug infusion) between the groups were analysed with the Kruskal–Wallis test followed by Dunn’s multiple comparisons test. Correlations between the CI and Cp, K-ICG and Cp, BIS and Cp, ΔCI and ΔCp, ΔK-ICG and ΔCp, and ΔBIS and ΔCp were calculated using a linear regression analysis. The number of patients is indicated by n. A P-value of <0.05 was considered statistically significant. All data are presented as median (range).

**Results**

Thirty-eight female patients were included in the present study. One patient in the remifentanil 0 µg kg⁻¹ min⁻¹...
group was excluded because the BIS did not decrease below 65 just before tracheal intubation. One patient in the remifentanil 0 μg kg⁻¹ min⁻¹ group was excluded because the K-ICG could not be measured due to an ICG excretory disturbance. Patient characteristics are summarized in Table 1. No significant difference was observed between the groups. Body temperature was preserved within 0.5°C in all patients.

The effects of remifentanil on MAP, HR, CI, BV, K-ICG, BIS, and Cp are shown in Table 2. Before infusion of saline or remifentanil, there was no significant difference between the groups. In the remifentanil 0 μg kg⁻¹ min⁻¹ group, HR, BIS, and K-ICG significantly decreased in comparison with the levels before saline infusion. In the remifentanil 0.5 μg kg⁻¹ min⁻¹ group, MAP, HR, CI, BV, and K-ICG decreased significantly, whereas there was no significant change in BIS or Cp. Compared with remifentanil 0 μg kg⁻¹ min⁻¹, remifentanil 0.5 μg kg⁻¹ min⁻¹ significantly decreased the HR. In the remifentanil 1.0 μg kg⁻¹ min⁻¹ group, MAP, HR, CI, and K-ICG decreased significantly and Cp increased significantly 15 min after remifentanil infusion compared with before remifentanil infusion. Compared with remifentanil 0 μg kg⁻¹ min⁻¹, remifentanil 1.0 μg kg⁻¹ min⁻¹ decreased MAP, HR, and K-ICG and Cp increased significantly.

Figure 1 shows the effect of remifentanil on ΔCI, K-ICG, Cp, and BIS. CI decreased significantly in the remifentanil 0.5 and 1.0 μg kg⁻¹ min⁻¹ groups compared with that in the remifentanil 0 μg kg⁻¹ min⁻¹ group (Fig. 1A, P<0.0001, respectively). K-ICG was significantly decreased in the remifentanil 1.0 μg kg⁻¹ min⁻¹ group compared with that in the remifentanil 0 μg kg⁻¹ min⁻¹ group (Fig. 1B, P<0.05). Cp was significantly increased in the remifentanil 1.0 μg kg⁻¹ min⁻¹ group compared with that in the remifentanil 0 μg kg⁻¹ min⁻¹ group (Fig. 1C, P<0.05). ΔBIS was significantly higher in the remifentanil 0.5 μg kg⁻¹ min⁻¹ group compared with that in the remifentanil 0 μg kg⁻¹ min⁻¹ group (Fig. 1D, P<0.05).

Figure 2 shows the linear correlations and the correlation coefficients between Cp and CI (Fig. 2A) and ΔCp and ΔCI (Fig. 2B). ΔCp significantly increased with a decrease in ΔCI (P<0.05). Figure 3 shows the linear correlations and the correlation coefficients between K-ICG and Cp (Fig. 3A) and ΔCp and ΔK-ICG (Fig. 3B). Cp and ΔCp increased significantly with a decrease in the K-ICG and ΔK-ICG (both P<0.05).

### Table 1 Patient characteristics. Values are median (range). There were no significant differences among the three groups

<table>
<thead>
<tr>
<th>Remifentanil (μg kg⁻¹ min⁻¹)</th>
<th>0</th>
<th>0.5</th>
<th>1.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>43 (21–63)</td>
<td>39 (22–67)</td>
<td>44 (29–69)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>54 (45–71)</td>
<td>53 (67–40)</td>
<td>53 (42–64)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>160 (150–165)</td>
<td>155 (149–165)</td>
<td>158 (149–166)</td>
</tr>
</tbody>
</table>

### Table 2 Changes in MAP, HR, CI, BV, K-ICG, and Cp. MAP, mean arterial pressure; HR, heart rate; BIS, bispectral index; CI, cardiac index; BV, blood volume; K-ICG, indocyanine green disappearance ratio; Cp, plasma propofol concentration; Pre, values before remifentanil infusion; Post, values 15 min after remifentanil infusion. Values are median (range). *, **, and *** indicate P<0.05, <0.01, and <0.001, respectively, vs pre values. †, ††, and ††† indicate P<0.05, <0.01, and <0.001, respectively, vs the 0 μg kg⁻¹ min⁻¹ remifentanil group

<table>
<thead>
<tr>
<th>Remifentanil (μg kg⁻¹ min⁻¹)</th>
<th>0</th>
<th>0.5</th>
<th>1.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAP (mm Hg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre</td>
<td>70 (61–84)</td>
<td>70 (60–86)</td>
<td>69 (62–98)</td>
</tr>
<tr>
<td>Post</td>
<td>68 (53–85)</td>
<td>61 (50–89)**</td>
<td>59 (44–63)***†††</td>
</tr>
<tr>
<td>HR (beats min⁻¹)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre</td>
<td>70 (55–78)</td>
<td>67 (58–75)</td>
<td>70 (54–73)</td>
</tr>
<tr>
<td>Post</td>
<td>66 (51–72)**</td>
<td>56 (47–62)***†††</td>
<td>54 (42–58)***†††</td>
</tr>
<tr>
<td>BIS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre</td>
<td>36 (26–45)</td>
<td>37 (23–47)</td>
<td>42 (25–56)</td>
</tr>
<tr>
<td>Post</td>
<td>31 (22–40)*</td>
<td>38 (22–51)</td>
<td>36 (30–48)</td>
</tr>
<tr>
<td>CI (litre min⁻¹ m⁻²)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre</td>
<td>2.6 (1.6–3.2)</td>
<td>2.8 (1.8–3.5)</td>
<td>2.6 (2.0–3.9)</td>
</tr>
<tr>
<td>Post</td>
<td>2.4 (1.7–3.1)</td>
<td>2.1 (1.4–2.9)***</td>
<td>2.0 (1.6–2.7)***</td>
</tr>
<tr>
<td>BV (litre)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre</td>
<td>3.4 (2.5–3.7)</td>
<td>3.6 (2.4–4.3)</td>
<td>3.6 (2.8–5.4)</td>
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<tr>
<td>Post</td>
<td>3.4 (2.5–4.2)</td>
<td>3.3 (2.2–4.3)**</td>
<td>3.2 (2.9–4.4)</td>
</tr>
<tr>
<td>K-ICG (min⁻¹)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre</td>
<td>0.23 (0.20–0.27)</td>
<td>0.23 (0.18–0.26)</td>
<td>0.22 (0.16–0.28)</td>
</tr>
<tr>
<td>Post</td>
<td>0.21 (0.19–0.24)*</td>
<td>0.21 (0.16–0.25)**</td>
<td>0.18 (0.15–0.23)***†</td>
</tr>
<tr>
<td>Cp (μg ml⁻¹)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre</td>
<td>2.4 (2.2–3.2)</td>
<td>2.6 (2.1–3.3)</td>
<td>2.5 (1.7–3.7)</td>
</tr>
<tr>
<td>Post</td>
<td>2.3 (1.6–3.2)</td>
<td>2.7 (2.1–4.2)</td>
<td>3.0 (2.1–3.7)***†</td>
</tr>
</tbody>
</table>
Figure 4 shows the linear correlations and the correlation coefficients between BIS and Cp (Fig. 4A) and ΔBIS and ΔCp (Fig. 4B). Data pairs 15 min after saline or remifentanil infusion were included in these analyses.

Discussion

During propofol TCI in the absence of surgical stimulation, remifentanil coadministration significantly suppressed MAP and HR along with a significant decrease in CI. Remifentanil significantly decreased K-ICG, indicating that liver blood flow may be reduced by remifentanil. Cp increased significantly with a decrease in K-ICG, suggesting that the increase in Cp induced by remifentanil is associated with a decrease in propofol clearance by the liver. Although remifentanil increased the Cp, there was no significant decrease in BIS in the present study.

Propofol concentration is influenced by CO and there is an inverse relationship between CO and propofol concentration. Consequently, because remifentanil decreases arterial pressure, HR, and CO, we hypothesized that remifentanil increases the Cp. Bouillon and colleagues found no alterations in propofol pharmacokinetics during non-steady-state conditions. In contrast, our study shows that remifentanil suppressed CI and K-ICG, which was associated with an increase in Cp. Although this does not prove a direct causative correlation, it is suggestive of decreased liver perfusion with subsequent alterations in propofol pharmacokinetics.

A significant increase in Cp was observed only in the remifentanil 1.0 \( \mu g \text{ kg}^{-1} \text{ min}^{-1} \) group, a relatively high dose in the clinical setting. Therefore, the clinical importance of the effect of remifentanil on Cp may be limited during propofol anaesthesia.

In the present study, we hypothesized that remifentanil increases Cp and reduces the BIS. We did not, however, observe a significant reduction in the BIS. One possible reason for the lack of a decrease in BIS values is deep anaesthesia. BIS values in the present study were relatively low and a burst suppression EEG pattern was observed in two patients. The increase in Cp in the present study may not have been sufficient to decrease BIS in such deep anaesthesia. Another possible reason for the lack of a decrease in BIS is the effect of remifentanil on the EEG parameters. Remifentanil has different effects on EEG parameters during propofol anaesthesia, depending on the depth of anaesthesia, which may increase the data variability of BIS. Remifentanil increased Cp, but there was no significant correlation between Cp and BIS and 0.5 \( \mu g \text{ kg}^{-1} \text{ min}^{-1} \) remifentanil, which significantly increased BIS. These findings indicate that the sensitivity of BIS for Cp may be low during remifentanil coadministration.

To achieve cardiovascular stability and a constant effect-site concentration of propofol, baseline data were recorded 15 min after tracheal intubation. There were significant decreases in HR, K-ICG, and BIS, however, even in the remifentanil 0 \( \mu g \text{ kg}^{-1} \text{ min}^{-1} \) group. In previous studies, the...
Fig 2 Relationship between the CI and Cp. (a) There was no statistically significant correlation between Cp and CI \((P=0.56, r=0.10)\). \(Cp=-0.12 \times CI+2.97\), resulting in a correlation coefficient of 0.10. (a) The relationship between changes in CI \((\Delta CI)\) and Cp \((\Delta Cp)\). The solid line indicates a linear relationship between \(\Delta CI\) and \(\Delta Cp\) \((P=0.0001, r=0.59)\). \(\Delta Cp=-0.56 \times \Delta CI+0.10\), resulting in a correlation coefficient of 0.33. White, green, and pink circles represent individual patients in the 0, 0.5, and 1.0 \(\mu g\) kg\(^{-1}\) min\(^{-1}\) remifentanil groups, respectively. Data pairs 15 min after saline or remifentanil infusion were included in these analyses.

Fig 3 Relationship between the K-ICG and the Cp. (a) The solid line shows the linear relationship between K-ICG and Cp \((P<0.05, r=0.16)\). \(Cp=-9.06 \times K-ICG+4.54\), resulting in a correlation coefficient of 0.40. (a) The relationship between the changes in K-ICG \((\Delta K-ICG)\) and changes in Cp \((\Delta Cp)\). The solid line shows the linear relationship between \(\Delta CI\) and \(\Delta Cp\) \((P<0.05, r=0.33)\). \(\Delta Cp=-5.40 \times \Delta K-ICG+0.05\), resulting in a correlation coefficient of 0.33. White, green, and pink circles represent individual patients in the 0, 0.5, and 1.0 \(\mu g\) kg\(^{-1}\) min\(^{-1}\) remifentanil groups, respectively. Data pairs 15 min after saline or remifentanil infusion were included in these analyses.

Fig 4 Relationship between the Cp and BIS. (a) There was no statistically significant correlation between Cp and BIS \((P=0.31, r=0.18)\). \(BIS=2.16 \times Cp+28.9\), resulting in a correlation coefficient of 0.18. (a) The relationship between the changes in Cp \((\Delta Cp)\) and changes in BIS \((\Delta BIS)\). There was no statistically significant correlation between Cp and CI \((P=0.27, r=0.19)\). \(\Delta BIS=4.05 \times \Delta Cp+3.70\), resulting in a correlation coefficient of 0.19. White, green, and pink circles represent individual patients in the 0, 0.5, and 1.0 \(\mu g\) kg\(^{-1}\) min\(^{-1}\) remifentanil groups, respectively. Data pairs 15 min after saline or remifentanil infusion were included in these analyses.
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cardiovascular parameters continued to change clinically after achieving a constant effect-site concentration of propofol via TCI\textsuperscript{11} and a relatively long time may be needed to achieve a steady-state effect-site concentration of propofol when TCI based on Marsh’s pharmacokinetic–dynamic model is used.\textsuperscript{22} Therefore, a 15-min period might not be long enough to achieve a haemodynamic and hypnotic steady state, which may have increased the data variability in the present study. Although Cp significantly correlated with a decrease in K-ICG, the correlation does not prove direct causation because Cp did not significantly increase with a significant decrease in K-ICG in the control group.

BIS is increased by noxious stimuli, such as electrical stimulation, surgical stimulation, or tracheal intubation.\textsuperscript{7,23,24} Conversely, remifentanil decreases BIS in the presence of noxious stimuli.\textsuperscript{1} The present study was performed in intubated patients, which is a limitation. The effect of noxious stimulation on our findings may be limited, however, because tracheal intubation was performed after administration of 8% lidocaine spray to the larynx and 4% lidocaine injection into the trachea, and all data were recorded in the absence of surgical stimuli in all patients.

In conclusion, remifentanil had a suppressive effect on HR, MAP, CI, and K-ICG, accompanied by a significant increase in Cp. Cp increased with a decrease in K-ICG, suggesting that the increase in Cp by remifentanil coadministration during propofol anaesthesia is related to a decrease in the propofol clearance from the liver. Remifentanil had no suppressive effect on BIS. Because BIS did not correlate with Cp during remifentanil infusion, anaesthetic depth should be carefully assessed when remifentanil is coadministered during propofol anaesthesia.

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Conflict of interest
None declared.

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