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Propofol sparing effect of remifentanil using closed-loop anaesthesia†

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Background. General anaesthesia is a balance between hypnosis and analgesia. We investigated whether an increase in remifentanil blood concentration would reduce the amount of propofol required to maintain a comparable level of anaesthesia in 60 patients undergoing ambulatory surgery.

Methods. Patients were allocated randomly to receive remifentanil to a target blood concentration of 2 ng ml^{-1} (low), 4 ng ml^{-1} (medium), or 8 ng ml^{-1} (high), administered by target-controlled infusion (TCI). After equilibration, propofol TCI was commenced in closed-loop control, with auditory evoked potentials (AEPex) as the input signal, aiming for an AEPex of 35. This was to ensure a comparable and unbiased level of anaesthesia in all patients.

Results. We found a dose-dependent decrease in propofol requirements with increasing remifentanil concentrations. The mean (95% CI) propofol target blood concentration during adequate anaesthesia was 4.96 (3.85–6.01) μg ml^{-1} in the low, 3.46 (2.96–3.96) μg ml^{-1} in the medium, and 3.01 (2.20–3.38) μg ml^{-1} in the high group. There was no significant difference when recovery end points were achieved between the groups. Cardiovascular changes were moderate, but most pronounced in the high concentration group, with a decrease in heart rate of 21% compared with baseline. The mean calculated effect site propofol concentration at loss of consciousness was 2.08 (1.85–2.32) μg ml^{-1}, and at recovery of consciousness was 1.85 (1.68–2.00) μg ml^{-1}.

Conclusions. This study confirms a synergistic interaction between remifentanil and propofol during surgery, whereas the contribution of remifentanil in the absence of stimulation seems limited. In addition, our results suggest that the propofol effect site concentration provides a guide to the value at which the patient recovers consciousness.

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General anaesthesia is a balance between hypnosis and analgesia.[1] Fentanyl and alfentanil are known to interact in a synergistic manner with propofol to produce general anaesthesia,[2 3] and increased concentrations of opioids result in less propofol being required to maintain a satisfactory level of anaesthesia.

Previous studies investigating the interaction between propofol and opioids have used patient movement or other clinical signs as indicators of inadequate anaesthesia to assess the effective concentration where 50% of patients were adequately anaesthetized (EC_{50}).[2 3] The present study used the Auditory Evoked Potential Index (AEPex) as the indicator of anaesthetic depth.[4] Propofol was then administered using a closed-loop anaesthesia system (CLAN)

†*Declaration of interest*: The authors state no conflicts with commercial corporate interests have occurred with the work submitted. Dr Schraag received lecturing honoraria in the past by AstraZeneca, the manufacturer of Diprivan, the propofol formulation used in the study. Professor Kenny was one of the developers of the target-controlled infusion (TCI) system used in the present study. The original TCI system was licensed by Glasgow University in 1992 to Zeneca who introduced it as the *Diprifusor* and then to AstraZeneca when the companies merged. Professor Kenny has acted as a consultant to Zeneca and AstraZeneca.

based on the value of the AEPex. This allowed an unbiased assessment of how much propofol was required to produce satisfactory anaesthesia in all patients at different target remifentanil concentrations. We studied whether increasing the plasma concentration of remifentanil would reduce the amount of propofol required to maintain a comparable level of anaesthesia. In addition, we compared the calculated blood and effect site concentrations of propofol at loss of consciousness (LOC) and recovery of consciousness (ROC).

Methods

After local hospital ethics committee approval and obtaining written informed consent, 60 unpremedicated patients were recruited into the study. They underwent day-case surgery for inguinal hernia repair, or varicose vein surgery involving a groin incision. Patients with impaired renal or hepatic function, psychiatric disorder, reduced hearing threshold, or a known history of chronic drug or alcohol abuse were excluded, as well as those who were pregnant or obese (body mass index >30 kg $(m^2)^{-1}$), or had had previous adverse reactions to general anaesthesia.

The patients were randomized prospectively into three groups (20 patients/group) using computer-generated random numbers. Each group received remifentanil to a low, medium, or high target concentration of 2, 4, or 8 ng ml^{-1}, respectively. Remifentanil was administered by a target-controlled infusion (TCI) to ensure a constant plasma target concentration. Mean maintenance infusion rates of remifentanil, which are approximately equivalent to these targets are 0.08, 0.15 and 0.3 μg kg^{-1} min^{-1}. The infusion device was based on the prototype 'Diprifusor' system used in previous studies.[5] It was modified to a 'Remifusor' by programming with the validated pharmacokinetic data set for remifentanil published by Minto and colleagues,[6] which adjusts for age, weight, and sex. The remifentanil target concentrations were kept stable at the respective values throughout the procedure until the end of surgery.

Routine monitoring and the EEG electrodes for AEPex recording were attached. A 20G i.v. canula was inserted and TCI remifentanil started at the respective target concentration. The patient was pre-oxygenated with oxygen 100% and when blood and effect site remifentanil concentrations were in equilibrium (8–10 min), anaesthesia was induced by TCI propofol using the pharmacokinetic parameter set of Marsh,[7] as incorporated into the 'Diprifusor'. The propofol effect site concentrations reported are calculated on the basis of an equilibration constant k_{e0} of 0.2 min^{-1} according to Billard[8] based on the Marsh pharmacokinetic model of propofol. This calculation is built into the commercial Diprifusor system and can be displayed. Propofol TCI was controlled by a closed-loop system (CLAN) based on AEPex, to ensure an unbiased and comparable level of anaesthesia as described previously.[9]

The value for the AEPex was recorded in the awake patient, and the AEPex value to control satisfactory anaesthesia was entered into the CLAN system. This value was set to 35 for all patients, as it was the mean value required to produce surgical anaesthesia in a previous study.[4] Anaesthesia was induced by setting the propofol target to 4 μg ml^{-1}. This target was increased by 0.5 μg ml^{-1} every 30 s until LOC. The CLAN system was started after equilibrium of blood and effect site concentrations, and controlled the administration of propofol to maintain an AEPex of 35 in all patients. Thereafter, control of anaesthesia was achieved by transmitting the target blood propofol concentration calculated by the CLAN algorithm to the infusion system and maintaining the measured AEPex close to the selected value of 35.

A laryngeal mask airway (LMA®)[‡] was inserted and the patient's lungs ventilated with oxygen-enriched air to an end-tidal carbon dioxide of 5 kPa. No neuromuscular block drugs were administered, so that patients could move if anaesthesia was inadequate. Postoperative analgesia was provided with a combination of ketorolac 0.4 mg kg^{-1} and a local anaesthetic block.

At the end of surgery, the propofol and remifentanil targets were set to zero and recovery was assessed by determining the time to: (i) adequate respiration, expressed as a stable ventilatory frequency of 10 and higher, (ii) the first voluntary movement, (iii) eye opening, (iv) response to verbal command, and (v) recall of date of birth. Duration of surgery, total dose of propofol and remifentanil used, and the propofol target concentrations administered by the CLAN system during adequate anaesthesia were obtained. The calculated blood and effect site concentrations of propofol at LOC and ROC were recorded.

Descriptive data are presented as means with 95% confidence interval (CI) and, in the case of data that were not normal distributed, median values with interquartile range, expressed graphically as box and whiskers plots. Estimation of sample size per group was undertaken beforehand to detect a difference in the propofol blood concentration of at least 0.5 μg ml^{-1} with a power of 0.8 and a probability value of P=0.05. This indicated 18 patients were needed per group, and we elected to study 20 patients. Statistical assessment for between-group differences was accomplished with one-way analysis of variance (ANOVA) and the Kruskall–Wallis test, respectively, for skewed data. Comparisons between LOC and ROC were accomplished with Student's t-test. Probability values <0.05% were considered statistically significant. Calculations were performed with SPSS® v. 8.0 (SPSS Science Inc., Chicago, IL, USA) and STATISTICA v.5.5a (StatSoft, Tulsa, USA).

[‡]LMA® is the property of Intavent Ltd.

Table 1 Physical characteristics of patients, by treatment groups. Mean, 95% CI. *P*-value based on ANOVA

Remifentanil C_t	2 ng ml^{-1}	4 ng ml^{-1}	8 ng ml^{-1}	*P*-value
Age (yr)	42.9 (37.5–48.3)	40.4 (34.6–46.2)	41.5 (35.6–47.5)	0.81
Weight (kg)	69.8 (65.3–74.3)	71.9 (66.7–77.2)	69.2 (62.6–75.7)	0.73
Height (cm)	171.1 (166.0–176.1)	168.3 (163.9–172.5)	171.9 (167.8–175.9)	0.46
Sex (m/f)	9/11	12/8	9/11	—
ASA (1/2)	19/1	18/2	18/2	—

Table 2 Anaesthesia related variables. Mean, 95% CI. LOC denotes LOC. Drug dilutions were: propofol 10 mg ml^{-1} and remifentanil 20 μg ml^{-1}. *Statistically significant between groups (ANOVA)

Remifentanil C_t	2 ng ml^{-1}	4 ng ml^{-1}	8 ng ml^{-1}	*P*-value
Duration of anaesthesia (min)	40.7 (34.1–47.4)	43.4 (38.7–48.1)	48.2 (40.2–56.2)	0.25
Time on CLAN (min)	34.8 (28.1–41.5)	38.4 (33.7–43.1)	42.8 (34.8–50.7)	0.21
Baseline AEPex	70.2 (64.0–76.4)	69.3 (64.3–74.3)	69.1 (62.2–75.9)	0.95
Mean AEPex	35.4 (34.1–36.7)	35.1 (34.3–35.9)	35.7 (34.4–36.9)	0.74
Propofol consumption (ml)	67.4 (53.7–80.9)	57.3 (49.6–65.0)	51.2 (40.3–62.2)	0.11
Remifentanil consumption (ml)	11.8 (9.8–13.7)	25.4 (23.0–27.7)	54.4 (44.2–64.7)	<0.001*
Propofol C_t for LOC during induction	6.1 (5.5–6.6)	5.9 (5.5–6.4)	5.1 (4.8–5.4)	0.004*
Propofol C_t for adequate anaesthesia	4.96 (3.85–6.01)	3.46 (2.96–3.96)	3.01 (2.20–3.83)	0.003*

Table 3 Recovery related endpoints in minutes, by treatment groups. Mean, 95% CI. Adequate respiration was defined as a stable respiration rate of 10 min^{-1} and higher. *P*-value based on ANOVA

Remifentanil C_t	2 ng ml^{-1}	4 ng ml^{-1}	8 ng ml^{-1}	*P*-value
Adequate respiration	8.6 (6.9–10.2)	9.0 (7.5–10.5)	10.2 (7.8–12.5)	0.43
First movement	10.6 (8.4–12.7)	8.9 (7.5–10.2)	10.2 (7.6–12.8)	0.44
Eye opening	10.9 (8.7–13.0)	9.5 (8.0–11.1)	10.5 (7.9–13.2)	0.64
Obey commands	11.3 (9.1–13.4)	9.7 (8.2–11.2)	11.1 (8.5–13.7)	0.48
State date of birth	12.2 (9.8–14–5)	10.6 (8.9–12.1)	11.6 (9.1–14.8)	0.54

Table 4 Haemodynamic variables during the procedure compared with baseline values (start). Mean, 95% CI. *Statistically significant between groups (ANOVA)

Remifentanil C_t	2 ng ml^{-1}	4 ng ml^{-1}	8 ng ml^{-1}	*P*-value
Start heart rate (beats min^{-1})	78.7 (71.4–86.1)	74.9 (68.2–81.7)	73.8 (67.4–80.2)	0.56
Mean heart rate (beats min^{-1})	65.3 (60.6–69.9)	61.8 (59.1–64.6)	58.3 (55.7–60.9)	0.016*
Start systolic arterial pressure (mm Hg)	148.6 (136.4–159.9)	142.2 (134.2–150.1)	136.6 (127.8–145.5)	0.22
Mean systolic arterial pressure (mm Hg)	105.2 (99.7–110.6)	99.7 (94.2–105.2	93.6 (87.8–99.5)	0.013*
Start diastolic arterial pressure (mm Hg)	89.5 (81.9–96.9)	86.8 (82.7–90.8)	84.3 (78.6–90.0)	0.44
Mean diastolic arterial pressure (mm Hg)	62.7 (57.4–68.1)	59.1 (55.1–63.0)	53.4 (49.8–56.9)	0.01*

Results

Patients ranged in age from 16 to 70 yr and were ASA I or II. The physical characteristics of the study population were comparable between groups and are summarized in Table 1. While the duration of anaesthesia and time receiving CLAN were comparable in the three treatment groups (Table 2), we found a dose-dependent decrease in propofol requirements with increasing remifentanil concentrations during surgical stimulation. This was expressed as significantly reduced propofol target concentrations in the presence of increasing concentrations of remifentanil during adequate CLAN (Table 2). The effect of different remifentanil concentrations on propofol requirements during the induction phase in the absence of any noxious stimulation was less pronounced, although we found a statistically significant difference in C_t at LOC. A comparable anaesthetic state was confirmed by similar AEPex values in all three groups both at baseline and during surgical anaesthesia.

The choice of combination between the hypnotic and analgesic component did not much influence the speed of recovery. The medium remifentanil group recovered slightly faster than the other two groups, although the absolute differences in minutes to reach the recovery

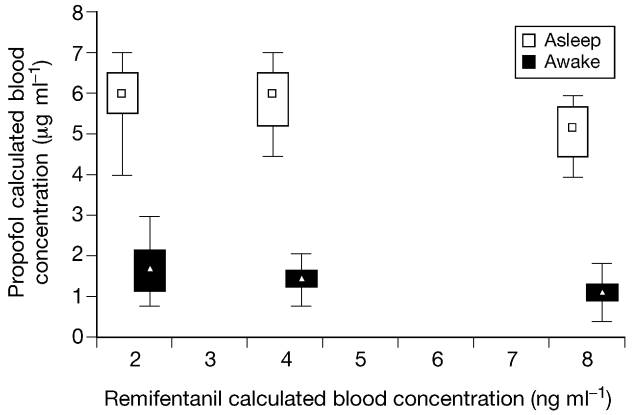

Fig 1 Calculated propofol blood concentration (μg ml^{-1}) during LOC and during awakening. *x*-axis refers to three different remifentanil groups studied, which are displayed on a linear scale of calculated remifentanil blood concentration (ng ml^{-1}). Data are expressed with box and whiskers plot around median values.

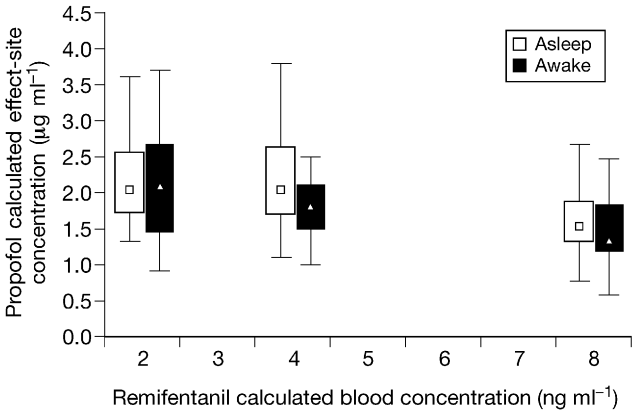

Fig 2 Calculated propofol effect site concentration (μg ml^{-1}) during LOC and during awakening. The *x*-axis refers to three different remifentanil groups studied, which are displayed on a linear scale of calculated remifentanil blood concentration (ng ml^{-1}). Data are expressed with box and whiskers plot around median values.

endpoint criteria were not statistically significant and presumably not clinically relevant (Table 3).

In contrast, we observed differences in the cardiovascular changes between groups (Table 4). In particular, the heart rate decreased significantly with increasing remifentanil concentrations, despite the use of less propofol. However, the absolute difference between groups remained small and, with overlapping confidence intervals, probably less meaningful. Similarly, both mean systolic and diastolic arterial pressures showed a moderate dose-dependent decrease. The greatest change from baseline values was observed in the high remifentanil group who received a target concentration of 8 ng ml^{-1}, where mean heart rate decreased by 21 compared with 17 and 15% in the medium and low groups, respectively.

With respect to propofol concentrations at loss and ROC, we observed a greater spread of data within the groups compared with the stage of stable anaesthesia during CLAN as expressed in Table 2. Figure 1 shows the distribution of propofol blood concentration in those patients at LOC compared to the values at ROC. These differences were not found if the respective calculated propofol effect site concentrations were compared at identical clinical end points (Fig. 2). The mean (95% CI) $C_{e\ prop}$ at LOC was 2.08 (1.85–2.32) μg ml^{-1}, and was 1.85 (1.68–2.00) μg ml^{-1}, slightly lower, at ROC (P=0.38). The individual calculated $C_{e\ prop}$ in patients losing and recovering consciousness were closely related with a mean (95% CI) absolute difference of 0.68 μg ml^{-1} (0.52–0.83), which is expressed in Figure 3. In 80% of patients, the absolute difference between LOC and ROC value was ⩽1 μg ml^{-1}, in 40% ⩽0.5 μg ml^{-1} and in 6% zero. The remifentanil concentration related decrease in mean $C_{e\ prop}$ was statistically significant between the groups (P=0.029 for LOC and P=0.001 for ROC).

Again, there is a remifentanil concentration-dependent effect in decreasing the respective propofol concentration both for losing and regaining consciousness, which is statistically significant.

Discussion

The combination of propofol with remifentanil as the analgesic component is becoming increasingly popular for providing general anaesthesia. Whereas dosing guidelines for fentanyl or alfentanil have been established empirically in the past and subsequently supported by studies,[2 3] there is a lack of knowledge about how to assess the requirements for remifentanil during surgical anaesthesia. Based on the results of isobolographic interaction studies, by which the character of interaction for different clinical endpoints can be assessed with a probabilistic approach[10] or, as introduced previously, by a response surface model,[11] the aim of the present study was to evaluate whether increasing the plasma concentration of remifentanil would reduce the amount of propofol, similar to that predicted by the interaction model, while maintaining a comparable level of anaesthesia.

We demonstrated a dose-dependent decrease in propofol requirements with increasing remifentanil concentrations both during adequate anaesthesia and for awakening. These results are principally in accordance with the interaction pattern suggested by Vuyk and colleagues,[10] as shown in Figure 4. However, besides these similarities there are some conflicting points, which have to be considered. In the original paper from Vuyk and colleagues,[3] the calculation of the effective concentration 50% (95%, respectively) was based on haemodynamic changes and the presence or absence of autonomic signs in paralysed patients during alfentanil–propofol anaesthesia for lower abdominal surgery. They transposed their results[10] to generate a corresponding propofol–remifentanil interaction curve based on an equipotency ratio of alfentanil:remifentanil of 30:1 (Fig. 4). Although it has been shown that haemodynamic and autonomic variables have a low predictive value in assessing the depth of anaesthesia,[12] it is of interest that our

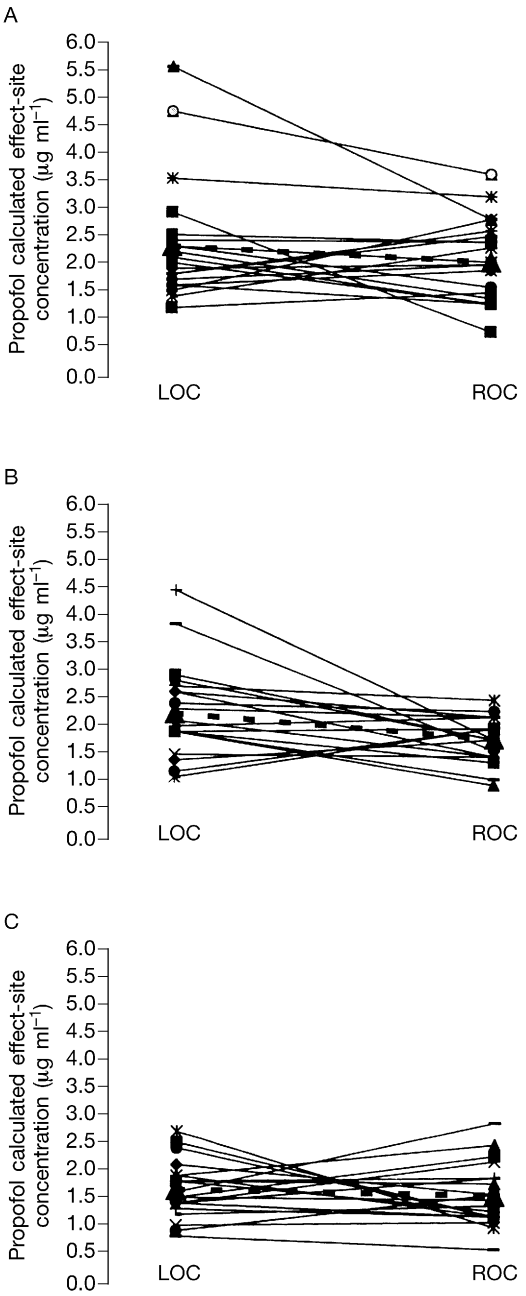

Fig 3 Propofol calculated effect site concentrations (μg ml^{-1}) at loss (LOC) and recovery (ROC) of consciousness, either in the presence of low (A) (2 ng ml^{-1}), medium (B) (4 ng ml^{-1}), or high (C) (8 ng ml^{-1}) remifentanil target blood concentrations. Individual patients are indicated with different symbols. The dotted line refers to the mean values for each group.

results are quite close to the predicted values of remifentanil–propofol interaction but with some exceptions which need to be discussed.

As the propofol concentrations obtained in our study represent the mean values of all patients having satisfactory anaesthesia, they would be expected to be greater than the $EC/CP_{95/50}$ values published by Vuyk and colleagues. This is only true in the group receiving high dose remifentanil (8 ng ml^{-1}), whereas the medium (4 ng ml^{-1}) and low (2 ng ml^{-1}) groups required less propofol than the EC/CP_{95} predicted from the Vuyk study. Similarly, we found different results with respect to awakening concentrations. Our findings of only minor differences between the groups in the calculated propofol concentrations when the patients recovered consciousness (1.2 μg ml^{-1} in high, 1.5 μg ml^{-1} in medium, 1.7 μg ml^{-1} in low remifentanil group) are consistent with the limited hypnotic potencies of opioids, even in higher concentrations. This may have been overestimated by the calculated interaction in Vuyk's report. Again, we report mean values for all patients recovering consciousness rather than EC/CP_{50} values (Fig. 4). Possibly, the equipotency ratio between alfentanil and remifentanil may be greater than 30:1. We studied patients undergoing minor ambulatory surgical procedures, whereas Vuyk's group studied patients undergoing lower abdominal surgery. This difference in the level of surgical stimulation may have contributed to the different results between the studies. In addition, all our patients received infiltration of local anaesthetic into the incision sites at the end of surgery, which would have decreased the stimulating effect of surgery on patient arousal and allowed our patients to recover at lower propofol and remifentanil concentrations. Whereas Vuyk and his colleagues used clinical signs to indicate inadequate anaesthesia, the present study was CLAN controlled by the AEPex, which may be less sensitive to graded changes in the concentrations of opioids.[13]

In contrast to previous interaction studies, we used AEP as a surrogate measure of anaesthesia effect. AEP are associated with a high validity to detect arousal during surgery,[4] and to discriminate the conscious from the unconscious patient.[14] Both criteria have been suggested as preconditions to providing adequate anaesthesia.[15] The use of AEPex as the input signal for feedback closed-loop control of propofol administration in 100 spontaneously breathing patients has been validated previously.[9] Although it may be difficult to show clinical advantages of closed-loop systems over conventional, manually adjusted techniques of anaesthetic administration,[16] CLAN provides an unbiased method to maintain a comparable level of anaesthesia. It is therefore suitable to act as a clinically relevant method to quantify interactions across the whole period of anaesthesia from induction to emergence.

An important observation seen in each of the three groups was the highly variable propofol target concentrations during the induction period of CLAN, regardless of the remifentanil concentration present. The lack of major differences in propofol requirements between the three groups in the early induction phase was likely to be caused by poor hypnotic potency, and therefore a limited contribution of remifentanil to controlling the AEPex in the absence of surgical stimulation. In contrast, the effect of higher remifentanil concentrations during the subsequent phase of anaesthesia where surgical stimulation was present

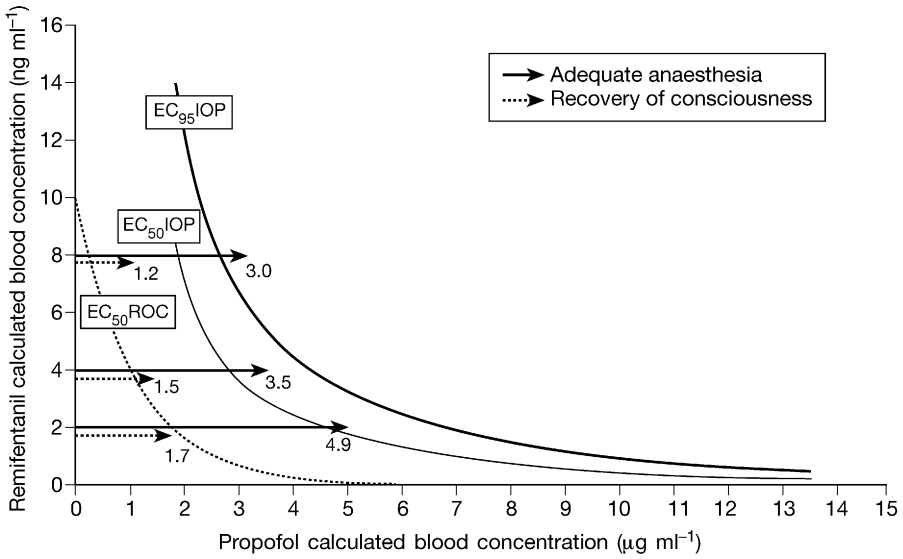

Fig 4 Synergistic interaction of remifentanil and propofol. Relationship of effective concentration 95% for intraoperative stimulation, effective concentration 50% for intraoperative stimulation, and effective concentration 50% for ROC. The curves are based on calculated interaction pattern published by Vuyk and colleagues.[10] They are compared with the results from the present study by plotting arrows with the respective values for adequate anaesthesia (filled arrows) and ROC (dotted arrows). Mean values in μg ml^{-1}.

was demonstrated by the concentration-dependent reduction of the absolute propofol target concentration values.

It is recognized that increasing the remifentanil concentration may be responsible for the development of haemodynamic depression, especially bradycardia. In a study investigating the cardiovascular response to laryngoscopy and intubation, Hall and colleagues administered remifentanil with or without glycopyrrolate and found a significant decrease in heart rate in the group without glycopyrrolate.[17] The calculated blood concentration of their infusion regime was 5–6 ng ml^{-1}, and therefore between our medium and high concentration group. However, even without pretreatment with glycopyrrolate, the maximum decrease in heart rate in our study was 21% compared with baseline in the high concentration group which, in the presence of only minor changes in arterial pressure, indicates a stable cardiovascular response to surgery.

The essence of all interaction studies involving opioids is that there is a synergistic interaction with propofol and, regardless which fentanyl congener is used, that the character of interaction depends on the clinical endpoints studied.[18] One of the most important endpoints when choosing remifentanil is the termination of the anaesthetic and the recovery of the patient. Computer simulations using pharmacokinetic parameters predict a more rapid and predictable recovery with remifentanil due to its short context-'insensitive' half-life of 3–4 min.[19] These pharmacokinetic simulations led to the suggestion that a high-dose remifentanil, low-dose propofol anaesthetic would result in the most rapid recovery while ensuring satisfactory anaesthesia beforehand. But is this concept supported clinically? We observed little difference in absolute recovery times between the low, medium, and high remifentanil group both for the emergence phase (adequate respiration, eye opening) and the intermediate recovery (obeying commands). However, the most rapid recovery for all observed clinical endpoints was seen in the medium dose group (remifentanil 4 ng ml^{-1}), although this difference was only in the range of 2–3 min. A similar recommendation was given by Vuyk and colleagues based on their simulation study[10]. O'Hare and colleagues investigated recovery after propofol–remifentanil anaesthesia using four different target concentrations of propofol and adjusting the remifentanil infusion during surgery.[20] They found a dose-dependent prolonging effect on early recovery with increasing propofol concentrations in a range between 6 and 14 min. This study also supports the use of higher remifentanil concentrations in the presence of rather low propofol concentrations when a rapid emergence is required.

In conclusion, we have shown the effect of altering the blood remifentanil concentration during propofol anaesthesia to be dose-dependent. The effect of reducing the required amount of propofol and altering the cardiovascular response during anaesthesia was most prominent with a relatively high remifentanil concentration, whereas emergence was only minimally affected with small differences in all recovery criteria. However, the pattern of interaction during surgery is dynamic, and thus the most rational approach that can be derived from this study appears to be titrating remifentanil in a concentration range between 4 and 8 ng ml^{-1}, but ensuring a minimum concentration of propofol, since the hypnotic property of remifentanil itself is limited.

The close relationship between the calculated effect site concentration of propofol at LOC and ROC suggests that, during surgery, the effect site propofol concentration should

always be maintained above the value when the individual patient loses consciousness. This demonstrates that the calculated effect site concentration is a more meaningful parameter to describe the clinical condition in a dynamic situation than the blood concentration. It would seem prudent to increase the maintenance effect site concentration above the value at LOC by at least 1 μg ml^{-1}, although further studies are necessary to confirm this relationship.

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