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Pharmacodynamic Interaction of Remifentanil and Dexmedetomidine on Depth of Sedation and Tolerance of Laryngoscopy

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EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- Patients sedated with standard clinical doses of dexmedetomidine can be readily aroused
- Dexmedetomidine doses producing mild to deep sedation lack significant analgesic effect
- Remifentanil is an opioid analgesic with only modest sedative properties
- Addition of remifentanil to propofol sedation reduces the propofol concentration required to reach tolerance of shaking the patient while shouting their name and tolerance of laryngoscopy

What This Article Tells Us That Is New

- This three-phase crossover trial to study the pharmacodynamic interaction between remifentanil and dexmedetomidine in 30 age- and sex-stratified healthy volunteers found that, despite falling asleep, most subjects remained arousable by calling their name, shaking the subject while shouting their name, or a trapezius squeeze, even after reaching supraclinical concentrations
- Adding remifentanil to dexmedetomidine sedation did not affect the likelihood of response to graded stimuli
- Dexmedetomidine potency increased with increasing age

ABSTRACT

Background: Dexmedetomidine is a sedative with modest analgesic efficacy, whereas remifentanil is an opioid analgesic with modest sedative potency. Synergy is often observed when sedative–hypnotics are combined with opioid analgesics in anesthetic practice. A three-phase crossover trial was conducted to study the pharmacodynamic interaction between remifentanil and dexmedetomidine.

Methods: After institutional review board approval, 30 age- and sex- stratified healthy volunteers were studied. The subjects received consecutive stepwise increasing target-controlled infusions of dexmedetomidine, remifentanil, and remifentanil with a fixed dexmedetomidine background concentration. Drug effects were measured using binary (yes or no) endpoints: no response to calling the subject by name, tolerance of shaking the patient while shouting the name ("shake and shout"), tolerance of deep trapezius squeeze, and tolerance of laryngoscopy. The drug effect was measured using the electroencephalogram-derived "Patient State Index." Pharmacokinetic–pharmacodynamic modeling related the administered dexmedetomidine and remifentanil concentration to these observed effects.

Results: The binary endpoints were correlated with dexmedetomidine concentrations, with increasing concentrations required for increasing stimulus intensity. Estimated model parameters for the dexmedetomidine EC50 were 2.1 [90% CI, 1.6 to 2.8], 9.2 [6.8 to 13], 24 [16 to 35], and 35 [23 to 56] ng/ml, respectively. Age was inversely correlated with dexmedetomidine EC50 for all four stimuli. Adding remifentanil did not increase the probability of tolerance of any of the stimuli. The cerebral drug effect as measured by the Patient State Index was best described by the Hierarchical interaction model with an estimated dexmedetomidine EC_{50} of 0.49 [0.20 to 0.99] ng/ml and remifentanil EC_{50} of 1.6 [0.87 to 2.7] ng/ml.

Conclusions: Low dexmedetomidine concentrations (EC_{50} of 0.49 ng/ml) are required to induce sedation as measured by the Patient State Index. Sensitivity to dexmedetomidine increases with age. Despite falling asleep, the majority of subjects remained arousable by calling the subject's name, "shake and shout," or a trapezius squeeze, even when reaching supraclinical concentrations. Adding remifentanil does not alter the likelihood of response to graded stimuli.

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DEXMEDETOMIDINE is a sedative that acts through binding to the α2-adrenoceptor. Dexmedetomidine has the unusual property of providing significant sedation without cardiorespiratory compromise.[1] Additionally, patients sedated with dexmedetomidine can be readily aroused.[1] These features, combined with anxiolytic and amnestic effects, make dexmedetomidine useful in many procedures, such as procedural sedation, awake craniotomies, and postoperative and/or intensive care unit sedation. Side effects are mainly hemodynamic and include hypertension, hypotension, and bradycardia caused by vasoconstriction,

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sympatholysis, and baroreflex-mediated parasympathetic activation.[2,3]

In clinical anesthesia, hypnotics are frequently administered in combination with opioid analgesics. Combined drug effects can be synergistic, additive, or infraadditive.[4,5] The interaction is additive if the same drug effect is observed for a particular sum of the individual concentrations normalized to potency regardless of the ratio of the drugs to each other. Synergy is observed when the combination of two drugs, normalized to potency, produces a greater drug effect than an equivalent potency-normalized concentration of either drug alone. Rarely the combination of two drugs, normalized to potency, produces a lesser drug effect than an equivalent potency-normalized concentration of either drug alone. This is referred to as infraadditivity or antagonism. Quantifying drug interactions is important in the field of anesthesia and helps to develop better dosing regimens.

In previous interaction studies, dexmedetomidine has been shown to reduce requirements isoflurane,[6–8] sevoflurane,[9,10] propofol,[11–13] thiopental,[14–17] and fentanyl.[18] Studies investigating the sedative and analgesic properties of dexmedetomidine found that doses resulting in mild to deep sedation lack significant analgesic efficacy.[19,20] Therefore, to ensure patient comfort in painful procedures, dexmedetomidine is frequently combined with analgesic drugs. Remifentanil is an opioid analgesic with only modest sedative properties.[21] This trial was designed to study the pharmacodynamic interaction between dexmedetomidine and remifentanil and quantify the expected synergy to determine the combination of dexmedetomidine and remifentanil that (1) maintains an unarousable state of sedation and (2) allows subjects to tolerate noxious stimuli, including painful procedures, surgery, and laryngoscopy.

Materials and Methods

This investigator initiated trial was conducted at the Department of Anesthesiology at the University Medical Center Groningen, Groningen, The Netherlands, in accordance with the Declaration of Helsinki and in compliance with good clinical practice and the applicable regulatory requirements. Ethical approval was obtained from the independent medical ethics review committee (Medisch Ethische Toetsings Commissie) of the foundation Evaluation of Ethics in Biomedical Research (Stichting BEBO), Assen, The Netherlands. The study was registered in the ClinicalTrials.gov database (NCT03143972).

Patient Inclusion

After obtaining written informed consent and performing a standard health screening, 30 volunteers were included in this study. Subjects were stratified according to sex and age (18 to 34, 35 to 49, and 50 to 70 yr).

Exclusion criteria were a history of intolerance to dexmedetomidine or remifentanil, a body mass index greater than 30 kg/m^2 or less than 18 kg/m^2, pregnancy or currently breastfeeding, neurologic disorders, depression requiring treatment with anti-depressive drugs, psychosis, dementia, schizophrenia, alcohol or drug abuse, recent use of psychoactive medication, chronic use of more than 20 g of alcohol daily, any significant cardiovascular disease or risk factor, bilateral nonpatent arteria ulnaris, or any other relevant medical condition.

Study Design

In this three-phase crossover study, each volunteer was scheduled for two study sessions, with a wash-out of at least 1 week between both days. During the first study session, volunteers received dexmedetomidine administered using target-controlled infusion with stepwise increasing effect site target concentrations of 1, 2, 3, 5, and 8 ng/ml dexmedetomidine. On their second study session, after an appropriate washout (more than 1 week), these volunteers received a stepwise increasing remifentanil infusion targeting effect site concentrations of 1, 2, 3, 5, and 7 ng/ml. After an interval for remifentanil washout, volunteers received dexmedetomidine *via* target-controlled infusion with an effect site target of 2 ng/ml. After an appropriate equilibration time, remifentanil was added with stepwise increasing effect site target concentrations of 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, and 4.0 ng/ml, respectively. See also figure S1.1 in Supplemental Digital Content 1 (http://links.lww.com/ALN/C12) for a schematic overview of the infusion regimens. Throughout this work, these three study phases will be referred to as "dexmedetomidine phase," "remifentanil phase," and "interaction phase," respectively.

Study Procedures

Study participants were instructed not to use recreational drugs for 2 weeks before the study, not to smoke tobacco for 1 week, and not to consume alcohol for 2 days before each of their study days. All volunteers were instructed to fast from 6 h before the start of the planned study procedures. During the study a board-certified anesthesiologist and nurse anesthetist were responsible for the monitoring and safety of the volunteers, drug administration, and respiratory support. A complete anesthesia workstation was present in the room, as well as an anesthesia ventilator (specifications of indicated materials, devices, and software used in this study can be found in Supplemental Digital Content 2, http://links.lww.com/ALN/C13) enabling the anesthesia team to provide monitored anesthesia care, ventilatory support, and emergency care if needed. A research physician and research nurse were responsible for all other study procedures. Upon arrival, volunteers were connected to a vital sign monitor (Supplemental Digital Content 2, http://links.lww.com/ALN/C13). A 20-gauge IV cannula was placed for fluid administration, dexmedetomidine and remifentanil administration, and, if applicable, rescue

medication. A 20-gauge arterial cannula was placed under ultrasound guidance and local anesthesia for blood sampling and hemodynamic monitoring (Supplemental Digital Content 2, http://links.lww.com/ALN/C13). No premedication was administered. To monitor ventilation, including inspiratory oxygen fraction (F_{IO_2}) and end-tidal carbon dioxide, volunteers breathed spontaneously through a tight-fitting face mask attached to a circular breathing system of an anesthesia ventilator (Supplemental Digital Content 2, http://links.lww.com/ALN/C13) with a F_{IO_2} set to 25%. If deemed necessary, the anesthesiologist supported respiration by verbal stimulation, chin lift or jaw trust, pressure supported spontaneous breathing, or positive pressure ventilation.

Measures of Drug Effect

The cerebral drug effect of dexmedetomidine was measured using a processed electroencephalographic measure, the Patient State Index (PSI-2) (Supplemental Digital Content 2, http://links.lww.com/ALN/C13). The PSI is an electroencephalogram-derived index to monitor the depth of anesthesia, with a PSI score of 100 representing the awake state and a PSI score of 0 denoting no detectable electrical brain activity.

Sedation was assessed using the Modified Observers Assessment of Alertness and Sedation (MOAA/S) score (table 1). MOAA/S assessments were performed by the attending anesthesiologist. The MOAA/S score was linked to our binary response/no response endpoints as follows:

1. No response to calling the subject by name was defined as a MOAA/S score of less than 3
2. Tolerance of shaking the patient while shouting the name ("shake and shout") was defined as a MOAA/S score less than 2
3. Tolerance of deep trapezius squeeze was defined as a MOAA/S score of 0
4. Tolerance of laryngoscopy was defined as a MOAA/S score of 0 and the ability to obtain a Cormack–Lehane score of 3 or less *via* direct laryngoscopy[22]

To standardize the pinch force used during the MOAA/S assessments of tolerance of trapezius squeeze to 20 lbs/inch,[2] the anesthesiologist trained himself or herself in squeezing force with a bedside pinch gauge (Supplemental Digital Content 2, http://links.lww.com/ALN/C13).

Volunteers were placed in supine position and were asked to stay in bed and not to engage in activities or spontaneous speech except for the required responses to MOAA/S assessments. Volunteers were not stimulated except for the MOAA/S assessments, and low ambient noise was ensured throughout the study period. Baseline measurements of vital parameters were taken for 5 min before drug infusion.

Drug Administration

Volunteers received dexmedetomidine *via* target-controlled infusion (Supplemental Digital Content 2, http://links.lww.com/ALN/C13). This target-controlled infusion was based on the pharmacokinetic model developed by Hannivoort *et al.*[23] expanded with an equilibration rate constant (ke0) for the effect site of the MOAA/S estimated in the pharmacodynamic model by Colin *et al.*[24] To avoid hypertensive reactions, the infusion of dexmedetomidine was limited to 6 $\mu g \cdot kg^{-1} \cdot h^{-1}$ for the first three infusion steps and was increased to 10 $\mu g \cdot kg^{-1} \cdot h^{-1}$ for the two highest targets of 5 and 8 ng/ml. During the second study session, a computer-controlled infusion, based on the pharmacokinetic–pharmacodynamic model developed by Eleveld *et al.*,[25] was used to target remifentanil effect-site concentrations.

Before each increase in effect site target, MOAA/S was scored, a scheduled blood sample was taken for measurement of drug concentrations, and if the MOAA/S score was 0 or 1, tolerance of laryngoscopy was tested. The concentration targets and the measurements performed during a steady-state observation phase are shown schematically in Supplemental Digital Content 1, figures S1.1 and S1.2 (http://links.lww.com/ALN/C12).

Recovery Period

After reaching tolerance of laryngoscopy or after completion of all infusion steps, drug infusion was stopped, and the recovery period began. In addition, the infusion was stopped when one of the following stopping criteria was met and deemed clinically relevant by the attending anesthesiologist:

- 30% increase from baseline mean arterial blood pressure for more than 5 min
- 30% decrease from baseline mean arterial blood pressure for more than 5 min
- Heart rate below 40 beats/min for more than 5 min
- Changes in cardiac conduction or cardiac rhythm
- Any other safety reason as judged by attending anesthesiologist

If deemed necessary, a rescue dose of 0.5 mg of atropine was given, and the drug infusion was stopped. To maintain an acceptable blood pressure, volunteers were put in Trendelenburg position of approximately 15°. If this was not effective, a rescue dose of 5 mg of ephedrine was administered, and the drug infusion was stopped.

During the recovery period MOAA/S scores were assessed with a 2-min interval for the first 30 min and with a 10-min interval thereafter until volunteers reached two consecutive MOAA/S scores of 5 with a 10-min interval between measurements. Blood samples were collected at predefined time points (see Arterial Blood Sampling section below). If the volunteer met the discharge criteria of the hospital's postanesthesia care unit, he or she was discharged from the research unit after the last sample was taken.

Arterial Blood Sampling

Arterial blood samples were drawn at baseline and at pseudo-steady state before changing the target concentration. Once the infusion was stopped, dexmedetomidine samples were

drawn at 2, 5, 10, 20, 60, 120, 300, and 420 min in the first session. After the remifentanil-only session in the second study, blood samples were collected at 2, 5, 10, and 30 min after stopping the remifentanil infusion. After the dexmedetomidine and remifentanil interaction session in the second study, blood samples were collected at 2, 5, 10, 20, 30, 60, 120, and 300 min after stopping the infusions (at 60, 120, and 300 min, only dexmedetomidine assessment was performed).

Storage and Analysis of Blood Samples

Blood was collected in EDTA tubes (Supplemental Digital Content 2, http://links.lww.com/ALN/C13) and immediately stored on ice for a maximum of 60 min (dexmedetomidine) or 15 min (remifentanil). Afterwards, samples were centrifuged for 5 min at 1,754*g* at 4°C. Plasma was transferred into cryovials and stored at or below −20°C until analysis. For remifentanil, sample stability was improved by the addition of 1.5 μl of formic acid per milliliter of plasma before freezing.[26]

Dexmedetomidine and remifentanil concentrations were measured using ultra-high-performance liquid chromatography–mass spectrometry (Supplemental Digital Content 2, http://links.lww.com/ALN/C13).[23,26] The lower and upper limits of quantification were 0.05 and 20 ng/ml for both compounds with a coefficient of variation of less than 8% for dexmedetomidine and less than 9% for remifentanil (within the entire range of the quality control samples of 0.075 to 7.5 ng/ml). Samples that were thought to be above the upper limit of quantification were diluted with blank human plasma before the sample treatment.

Optimization of Trial Design

The design of the clinical trial was *a priori* optimized using optimal experimental design principles. As such, various trial designs and sample sizes were simulated and compared. The primary objective here was to find the minimal sufficient trial design that would allow us to estimate all parameters included in the hierarchical interaction model with sufficient precision. The hierarchical interaction model was used in trial design optimization, because this model structure was regarded most appropriate. This assumption is based on previous studies describing opioid–hypnotic interactions.[21,27] The hierarchical model implies that opioids on their own have no effect on tolerance of laryngoscopy but that opioids reduce the amount of hypnotic needed to reach tolerance of laryngoscopy.[21]

Simulations showed that using the currently proposed trial design, a trial population of 30 subjects undergoing two crossover study phases would suffice to meet the study objectives. The infusion scheme was based on an estimated EC50 of 4 ng/ml dexmedetomidine for tolerance of laryngoscopy as described by Kunisawa *et al.*[28] To account for potential differences between our study population and the population by Kunisawa *et al.*,[28] we chose to work with an adaptive trial design. Therefore, an interim analysis was planned after enrollment of the first five volunteers. The adaptive design allowed us to change the drug infusion scheme to maximize the possibility of attaining informative drug concentrations and responses for pharmacokinetic–pharmacodynamic modeling based on the responses measured in these volunteers. See also Supplemental Digital Content 3 (http://links.lww.com/ALN/C14) for an extensive description of the adaptive trial design.

Data Handling

Measured arterial concentrations of samples drawn during pseudo–steady-state observation phases were used in pharmacodynamic modeling, because they are assumed to adequately reflect effect-site concentrations. Throughout this work these concentrations will be referred to as steady-state concentrations. MOAA/S scores and laryngoscopy observations during these steady-state phases were included in the final data set. MOAA/S scores were used to define the endpoints no response to name called, tolerance of shake and shout, and tolerance of trapezius squeeze. For PSI, the median value of a 60-s measurement interval before the start of the MOAA/S assessments was used in our analysis. This measurement period was chosen to circumvent the confounding effect of arousal caused by the MOAA/S assessments on the PSI value.

Pharmacodynamic Modeling Strategy

Nonlinear mixed effects modeling was used to study the relationship between measured steady-state concentrations and clinical endpoints no response to name called, tolerance of shake and shout, tolerance of trapezius squeeze, tolerance of laryngoscopy, and PSI (PSI-2).

Modeling of Binary Variables (No Response to Name Called, Tolerance of Shake and Shout, Tolerance of Trapezius Squeeze, and Tolerance of Laryngoscopy). For the binary dependent variables (no response to name called, tolerance of shake and shout, tolerance of trapezius squeeze, and tolerance of laryngoscopy) models were fitted to the data using the first-order estimation algorithm in NONMEM with the LIKELIHOOD option. The hierarchical interaction model, shown in equations 1 and 2, was selected as our base model.

$$U = \frac{C_D}{EC50_D} \cdot \left(1 + \left(\frac{C_R}{EC50_R}\right)^{\gamma_R}\right) \quad (1)$$

$$P_{\text{tolerance of a stimulus}} = \frac{U^{\gamma_D}}{1 + U^{\gamma_D}} \quad (2)$$

In this interaction model, U is the combined potency of the concentration (C) of both drugs (D for dexmedetomidine and R for Remifentanil) normalized over the concentration inducing half the maximal effect (EC50). With γ_R and γ_D representing the steepness of the curves, *P* is the probability of tolerating an applied stimulus.

First, for each stimulus (no response to name called, tolerance of shake and shout, tolerance of trapezius squeeze, and tolerance of laryngoscopy), a full structural model was constructed. For this, four parameters ($EC50_R$, $EC50_D$, γ_R, and γ_D) were estimated. Subsequently, we attempted to simplify this model. The full and reduced models were compared using the likelihood ratio test. Modifications to the structural and/or covariate model were accepted only if they resulted in a significant change in the objective function value. An increase in objective function value was judged statistically significant at the 5% level if exclusion of a parameter increased the objective function value by more than 3.84 points. Nonsignificant parameters were removed from the model one by one.

For the binary outcomes, our objective was to predict the population probability of no response to each stimulus. The emphasis is not on the concentration response relationship of an individual subject, and therefore interindividual variability was not included in the parameter estimation (*i.e.*, naive pooling approach). Once the final structural model was found, the influence of covariates was evaluated by inclusion of the covariates in the model on the $EC50_D$ parameter. Patient covariates considered for inclusion in the model were: age, height, weight, and sex.

Modeling of the Patient State Index. For the continuous dependent variable PSI, the first-order conditional estimation algorithm with interaction was used. Different previously published interaction models were fitted to the data. These models included: the hierarchical interaction model,[21] the Greco interaction model,[29,30] the sigmoid E_{max}, and the E_{max} model.[31] In contrast to the Greco model, the hierarchical interaction model assumes no effect of remifentanil in absence of dexmedetomidine. The sigmoid E_{max} and E_{max} model were fitted to test the hypothesis of no interaction effect, *i.e.*, these models assume that only dexmedetomidine exerts an effect on PSI.

These structural models were compared using the Akaike information criterion, the model with the lowest Akaike information criterion was chosen as our base model. Interindividual variability in the population was modeled using an exponential model. Additive, proportional, and combined residual error models were evaluated.

At each stage, the quality of the model was evaluated using change in objective function value, precision of parameter estimates, and shrinkage in empirical Bayes parameter estimates. Goodness-of-fit was graphically evaluated by graphs of the individual or population predicted *versus* observed responses and graphs of the conditionally weighted residuals *versus* individual predictions. As a safeguard against overparameterization, the condition number was calculated and compared across models.[32]

We first tested different structural models to account for the interaction between dexmedetomidine and remifentanil. Subsequently, covariates were tested by introducing them into the model. The covariates considered were age, height, weight, and sex. We tested for significant covariates on the EC50 parameter(s) and the baseline PSI parameter. As a final check, log-likelihood profiling was performed using Pearl-speaks-NONMEM (Supplemental Digital Content 2, http://links.lww.com/ALN/C13).

Statistical Analysis

Estimated model parameters are documented as typical values with 90% confidence intervals. Model parameter estimation was done using NONMEM (Supplemental Digital Content 2, http://links.lww.com/ALN/C13), and confidence intervals were calculated based on 10,000 bootstrap samples for the models for no response to name called, tolerance of shake and shout, tolerance of trapezius squeeze, and tolerance of laryngoscopy. For the PSI model, confidence intervals were derived based on log-likelihood profiling using Pearl-speaks-NONMEM (Supplemental Digital Content 2, http://links.lww.com/ALN/C13). Clinical data are given as means and SD or as medians and ranges, where appropriate.

Results

We screened 48 healthy volunteers. Of these, we included 35 in the study. Five volunteers dropped out before the start of the second study session and were replaced. Two volunteers dropped out because of failure of arterial cannula placement at the start of the first study session, one because of failure of arterial cannula placement at the start of the second study session, one volunteer withdrew after the first study session, and one volunteer was too anxious during the first study session and was therefore taken out of the study. Our total of 30 volunteers completing both study sessions were stratified into three age categories (18 to 34, 35 to 49, and 50 to 70 yr) with five males and five females in each category. Volunteers ranged from 18 to 67 yrs of age, 49.2 to 98.3 kg, and 158 to 193 cm tall and had body mass indexes from 18.2 to 28.7 kg/m^2.

We collected 464 observations of MOAA/S, PSI, and concomitant plasma samples during steady-state observation phases for our analysis. This resulted in a median of 15.5 (range 6 to 20) MOAA/S scores per subject and a median of 2 laryngoscopy attempts (range 0 to 6) per subject. The raw data are shown in figure 1. In the dexmedetomidine phase, a total of 34 laryngoscopy attempts were performed in 22 subjects. Of those, tolerance of laryngoscopy was achieved in 13 subjects. In the interaction phase, a total of 43 laryngoscopy attempts were performed in 19 subjects. Of those, laryngoscopy was achieved in 15 subjects. The reasons for stopping the infusions are displayed in Supplemental Digital Content 1, figure S1.3 (http://links.lww.com/ALN/C12).

After the first five volunteers completed the study, an interim analysis was performed. In the dexmedetomidine phase, one of these five volunteers reached laryngoscopy at the 4 ng/ml target concentration, one reached laryngoscopy at 8 ng/ml, and three volunteers did not reach laryngoscopy.

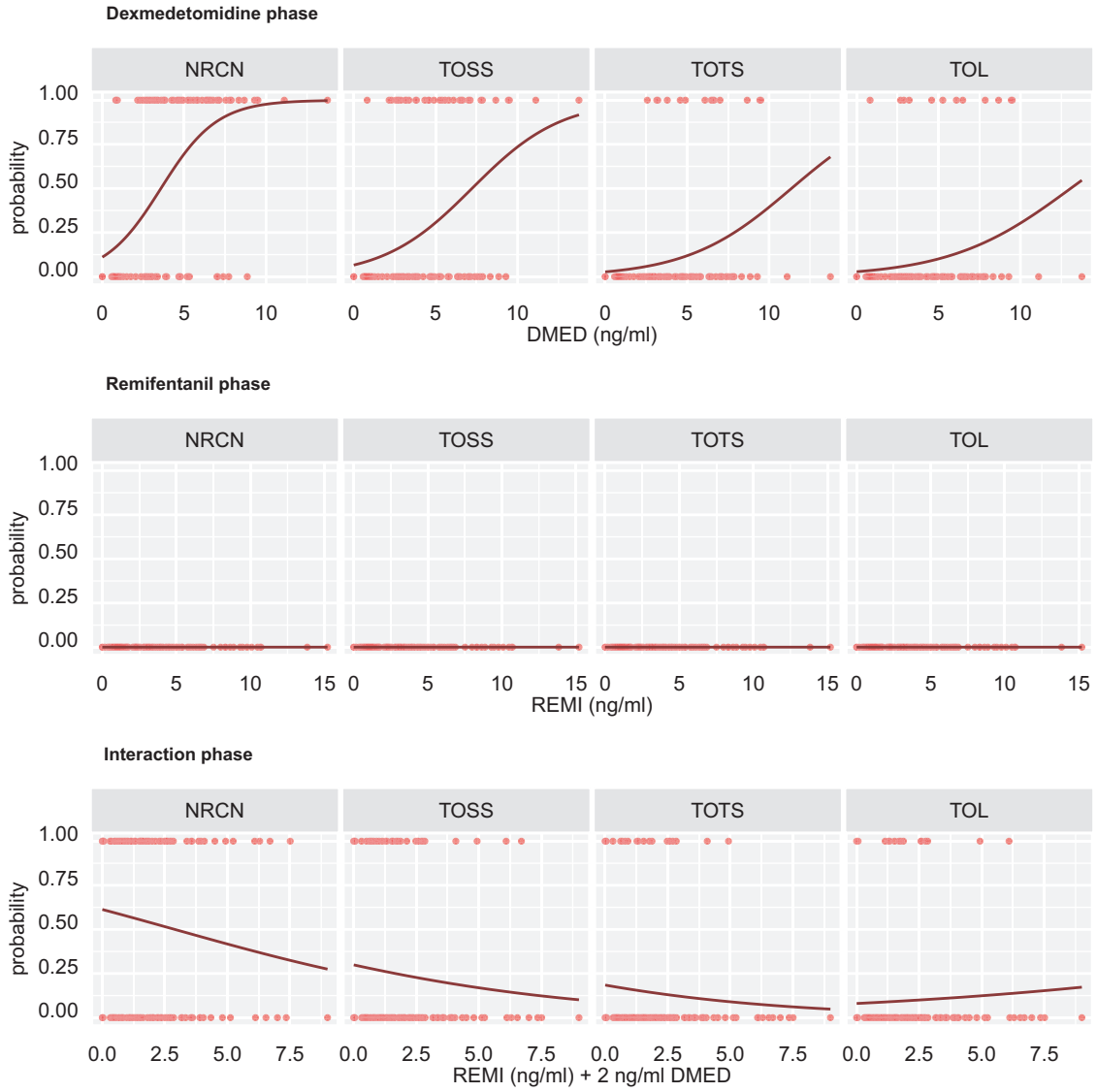

Fig. 1. All observations obtained during steady-state observation phases for no response to calling the subject by name (NRCN), tolerance of shake and shout (TOSS), tolerance of trapezius squeeze (TOTS), and tolerance of laryngoscopy (TOL), plotted *versus* measured dexmedetomidine (DMED) and remifentanil (REMI) concentrations. *Solid lines* denote a smoother obtained by fitting a generalized linear model through the data. For the interaction phase, remifentanil concentrations are plotted with 0 representing 0 ng/ml remifentanil but with a background concentration of 2 ng/ml dexmedetomidine being present.

According to the adaptive design flowchart (Supplemental Digital Content 3, figure S3.1 and tables S3.2, http://links.lww.com/ALN/C14), these results indicate a higher EC50 for tolerance to laryngoscopy than the 4 ng/ml estimated by Kunisawa *et al.*[28] and should have led to increasing the dexmedetomidine target concentrations. However, at the same time we observed long lasting hemodynamic side effects after stopping the dexmedetomidine infusion (hypotension and orthostatic hypotension). Therefore, for safety reasons, we decided not to increase target concentrations. Furthermore, because we noticed that our target-controlled infusion model underpredicted dexmedetomidine plasma concentrations at the 8.0 ng/ml target concentration, it was decided to lower the highest target level in the dexmedetomidine phase from 8.0 to 6.0 ng/ml. Of the first five volunteers who completed the interaction phase, four volunteers reached laryngoscopy at 1, 1.5, 1.5, and 2 ng/ml remifentanil, respectively. The concentration range seemed appropriately chosen and was not adjusted (Supplemental Digital Content 3, figure S3.2 and tables S3.3 and S3.4, http://links.lww.com/ALN/C14). Throughout the rest of the study, the design was not adjusted.

Accuracy of the Target-controlled Infusion Models Used in the Study

The predictive performances of the target-controlled infusion models were assessed by comparing predictions against the measured concentrations and calculating performance criteria according to Varvel *et al.*[33] Median performance errors of 27 and 5.7% and median absolute performance errors of 34 and 20% were calculated for dexmedetomidine infusion in the dexmedetomidine phase and interaction phase, respectively. Because nonlinearity in the pharmacokinetics of dexmedetomidine at high concentration rates may be present, a subanalysis was performed on the samples in the clinically used concentration range up to 3 ng/ml. When plasma samples with dexmedetomidine target-controlled infusion targets above 3 ng/ml and samples collected during the recovery of these high infusion targets were excluded from the analysis, the median absolute performance errors were 22 and 24%, and the median performance errors were 3.4 and 16% for the dexmedetomidine and the interaction phase, respectively. For remifentanil infusion, median performance errors of 3.6 and 35% and median absolute performance errors of 32 and 45% were calculated for the remifentanil phase and interaction phase, respectively. *Post hoc*, we also compared the performance of the applied models for dexmedetomidine and remifentanil to other available models using the drug infusion profiles from our study (Supplemental Digital Content 1, table S1.1, http://links.lww.com/ALN/C12).

Adverse Events

During the dexmedetomidine phase, obstructive breathing and obstructive apnea occurred in five subjects, of whom four were managed with manual airway maneuvers and one with a nasopharyngeal airway. The dexmedetomidine infusion was stopped because of hypertension in one subject and bradycardia in four subjects (Supplemental Digital Content 1, figure S1.3, http://links.lww.com/ALN/C12). Hypotension was countered with the Trendelenburg position and IV fluids in four subjects. Three hypotensive subjects required ephedrine 5 mg, one of whom received two boluses of ephedrine 5 mg. Dexmedetomidine infusion was stopped in one subject because of hypotension. Most subjects experienced prolonged periods of (asymptomatic) hypotension during the recovery period. The volunteers were given intravenous fluids, drinks, and food, and mobilizing was done slowly and carefully. Eight subjects experienced symptomatic orthostatic hypotension when they started mobilizing; two subjects required atropine 0.5 mg because of vagal responses.

During the remifentanil phase, 25 subjects developed ventilatory insufficiency with bradypnea and/or apnea, resulting in desaturations. These were managed mostly by verbally stimulating subjects to keep breathing (11 subjects), pressure support (9 subjects), and an increased F_{IO_2} (15 subjects). One subject's ventilation was briefly assisted manually, and one subject received a nasopharyngeal airway. Respiratory problems were a reason to stop the remifentanil infusion in six subjects. One subject developed ventilatory insufficiency with associated desaturation and developed severe opioid-induced muscle rigidity including thoracic rigidity, necessitating neuromuscular blockade, intubation, and sedation with propofol. All infusions were stopped, and she recovered uneventfully, but the interaction phase for this subject was cancelled. After the remifentanil infusion was stopped, 11 subjects developed nausea and received 4 mg ondansetron IV, and two subjects vomited.

During the interaction phase, obstructive breathing and apneas were recorded in 10 subjects, and ventilatory insufficiency with bradypnea and/or apnea was observed in two subjects. In this phase, drug infusions were stopped because of bradycardia in two subjects and because of hypotension in one subject. One subject received ephedrine 5 mg; the other nine cases of hypotension were managed with intravenous fluid and the Trendelenburg position. During the recovery period of the interaction phase, six subjects experienced symptomatic orthostatic hypotension, and two subjects experienced nausea.

Pharmacodynamic Models for No Response to Name Called, Tolerance of Shake and Shout, Tolerance of Trapezius Squeeze, and Tolerance of Laryngoscopy

First a complete hierarchical interaction model was fit to the data (equations 1 and 2), estimating four parameters per stimulus ($EC50_R$, $EC50_D$, γ_R, and γ_D). This resulted in an overparameterized model, with opioid γ and remifentanil EC50 parameters not simultaneously estimable. Therefore, the four opioid γ values were fixed to 1. The model was then further reduced by (1) estimating a single dexmedetomidine γ value (γ_D) across the different stimuli (where the change in objective function value was +1.74), (2) removal of the four interaction components from the model (where the change in objective function value was +3.85), and (3) fixing γ_D to 1 (where the change in objective function value was 0). The resulting structural model is shown in equation 3.

$$P_{\text{tolerance of a stimulus}} = \frac{\frac{C_D}{EC50_D}}{1+\frac{C_D}{EC50_D}} \quad (3)$$

Figure 1 shows the proportion of volunteers tolerating a stimulus as a function of the measured remifentanil concentrations during sole administration of remifentanil and during the interaction phase of our study. In analogy to our model-based findings, the figure shows no obvious effects of remifentanil on the probability of tolerance of any of the stimuli. The decreasing probabilities of no response to name called, tolerance of shake and shout, and tolerance of trapezius squeeze in the interaction phase, likely reflect the long stimulus-free interval preceding baseline observations (remifentanil = 0), in which we waited an hour for the wash-out of remifentanil and consecutively the equilibration of dexmedetomidine to

2 ng/ml, whereas the remaining observations were collected every 12 min.

Introducing age as a covariate significantly reduced in the objective function value (where the change in objective function value was 83.6). With age, dexmedetomidine EC50 decreases, showing an increasing sensitivity for dexmedetomidine with increasing age (fig. 2). The final model is described by equations 3 and 4. Parameter estimates and 90% confidence intervals are shown in table 2.

$$EC50_D = \mathrm{EC50}_{(Dtyp)} \cdot e^{(-0.0481 \cdot (AGE-35))} \quad (4)$$

Pharmacodynamic Model for PSI

PSI decreases with an increase in dexmedetomidine concentrations as shown in figure 3. For increasing remifentanil concentrations, the decrease in PSI is less pronounced. During the interaction phase, similar PSI values are seen across increasing remifentanil concentrations with a fixed dexmedetomidine background concentration of 2 ng/ml.

The Greco model had the lowest Akaike information criterion and was therefore initially retained for further model building. However, log-likelihood profiling consistently showed poor precision for the remifentanil EC_{50} and γ parameters in this model. Therefore, we also considered other models as starting points for model building. Of all models tested, the hierarchical model with interindividual variability on the EC_{50} parameters of remifentanil and dexmedetomidine had the lowest objective function value and was therefore retained as our final model. Visual inspection of the *post hoc* estimates for dexmedetomidine EC_{50} and PSI baseline did not show significant correlations to any of the covariates. Addition of these covariates to the model did not result in an improved goodness of fit.

Our final pharmacodynamic model for PSI is shown in equations 5 and 6. Parameter estimates and associated confidence intervals are shown in table 2. The response surface is shown in figure 4 and log-likelihood profiles and goodness-of-fit plots are presented in Supplemental Digital Content 1, figures S1.6 and S1.7 (http://links.lww.com/ALN/C12).

$$\mathrm{PSI}_{pred} = \mathrm{Base} \cdot \left(1 - \mathrm{E}_{max} \cdot \frac{\mathrm{U}^{\gamma_D}}{1 + \mathrm{U}^{\gamma_D}}\right) \quad (5)$$

$$\mathrm{U} = \frac{C_D}{EC_{50D}} \cdot \left(1 + \left(\frac{C_R}{EC_{50R}}\right)^{\gamma R}\right) \quad (6)$$

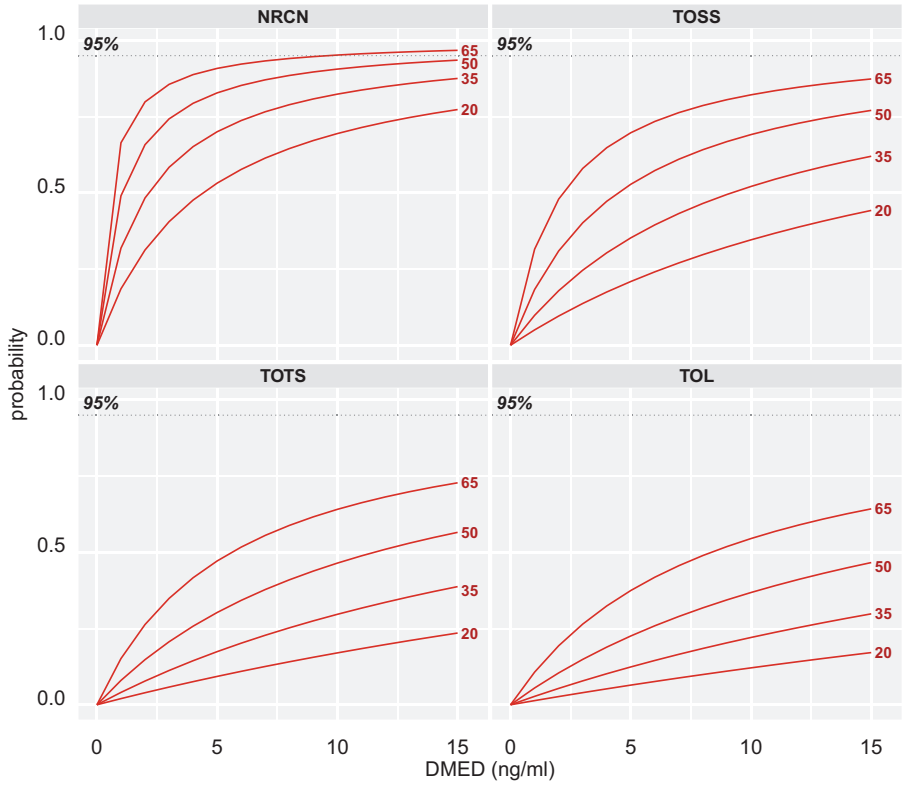

Fig. 2. Model predicted probabilities for no response to calling the subject by name (NRCN), tolerance of shake and shout (TOSS), tolerance of trapezius squeeze (TOTS), and tolerance of laryngoscopy (TOL) *versus* dexmedetomidine (DMED) concentrations. Probabilities are shown for 25-, 35-, 50-, and 65-yr-old subjects.

Table 1. Modified Observers' Assessment of Alertness and Sedation Score

Score	Response
5	Responds readily to name spoken in normal tone
4	Lethargic response to name spoken in normal tone
3	Responds only after name is called loudly and/or repeatedly
2	Responds only after mild prodding or shaking
1	Responds only after painful trapezius squeeze
0	No response after painful trapezius squeeze

For some volunteers in the remifentanil phase, the observed PSI values decreased below the PSI baseline predicted by the model. A graphical exploration of the data showed no clear relationship between PSI and measured remifentanil concentrations. We hypothesize that these measurements are due to remifentanil induced somnolence, a well known opioid side effect, causing the volunteers to fall asleep, thereby lowering the observed PSI values.

The Effect of Remifentanil on Arousability

For volunteers who tolerated laryngoscopy, the PSI values and MOAA/S scores recorded 5 min before and 2 to 3 min after laryngoscopy were compared. As shown in figure 5, PSI increased significantly after laryngoscopy in the dexmedetomidine phase, whereas a nonsignificant increase in PSI was seen in the interaction phase. In the dexmedetomidine phase, 7 of the 13 subjects who reached tolerance to laryngoscopy responded to name calling 2 to 3 min after the laryngoscopy. In the interaction phase, 4 of the 15 subjects who reached tolerance to laryngoscopy responded to name calling 2 to 3 min after the laryngoscopy attempt. Both the PSI and MOAA/S scores suggest attenuation of the arousal brought on by laryngoscopy in the interaction phase.

Discussion

The aim of this study was to investigate the pharmacodynamic interaction of dexmedetomidine and remifentanil to guide dosing during anesthesia and sedation. In this study, the estimated EC_{50} values of dexmedetomidine were 2.1, 9.2, 24, and 35 ng/ml for no response to name called, tolerance of shake and shout, tolerance of trapezius squeeze, and tolerance of laryngoscopy, respectively. Surprisingly, we found no additional effect of remifentanil on the probability of no response to these stimuli. Age was inversely correlated with the dexmedetomidine EC_{50} for all four stimuli, suggesting that subjects become more sensitive to dexmedetomidine with increasing age. The depth of sedation as measured by PSI was described best by the hierarchical interaction model with an estimated dexmedetomidine EC_{50} of 0.49 ng/ml and remifentanil EC_{50} of 1.6 ng/ml. In contrast to the high dexmedetomidine EC_{50} concentrations for no response to name called, tolerance of shake and shout, tolerance of trapezius squeeze, and tolerance of laryngoscopy, relatively low plasma concentrations of dexmedetomidine are required to induce sedation/hypnosis as measured by PSI. Because the hierarchical model fitted the data best, this indicates that the effect of remifentanil administered without dexmedetomidine is negligible. The remifentanil EC_{50} of 1.6 ng/ml for PSI drug effect shows that there is an effect of clinical doses of remifentanil on PSI, despite remifentanil's lack of effect on the probability of no response to for no response to name called, tolerance of shake and shout, tolerance of trapezius squeeze, and tolerance of laryngoscopy.

In the European Medicines Agency–approved drug label, dexmedetomidine infusion rates of 0.7 to 1.4 μg ·

Table 2. Parameter Estimates of the Final Models

	NRCN, TOSS, TOTS, and TOL				PSI				
	Estimate		90% CI		Estimate		90% CI		Shrinkage
THETA			Lower	Upper			Lower	Upper	
	$EC50_{D typ}$								
	$EC50_{D\ NRCN}$	2.1	1.5	3.0	$EC50_{D}$	0.49	0.20	0.99	
	$EC50_{D\ TOSS}$	9.2	7.0	13	$EC50_{R}$	1.6	0.87	2.7	
	$EC50_{D\ TOTS}$	24	16	38	γ_{D}	1.0	0.76	1.4	
	$EC50_{D\ TOL\_}$	35	25	54	γ_{R}	2.3	1.5	3.5	
					Base PSI	82	79	84	
					E_{max}	0.75	0.73	0.77	
Covariate	Age	−0.048	−0.079	−0.028					
ETA					IIV_$EC50_{D}$	3.0	1.5	6.6	[10%]
					IIV_$EC50_{R}$	0.91	0.32	2.7	[32%]
RUV					Prop. error	0.041	0.036	0.048	[4%]

Base PSI, baseline PSI value; CI, confidence interval derived through bootstrap sampling (NRCN, TOSS, TOTS, and TOL model) and through log-likelihood profiling (PSI model); $EC50_{D/R}$, half-maximal effective concentration of dexmedetomidine/remifentanil; $EC50_{D typ}$, concentration dexmedetomidine at which the probability of a typical individual (35 yr old) tolerating a stimulus is 50%; ETA, interindividual variability on parameter estimates; IIV, interindividual variability; NRCN, no response to calling by name; Prop. error, proportional error; PSI, Patient State Index; RUV, residual unexplained variability; THETA, parameter estimates; TOL, tolerance of laryngoscopy; TOSS, tolerance of shake and shout; TOTS, tolerance of trapezius squeeze.

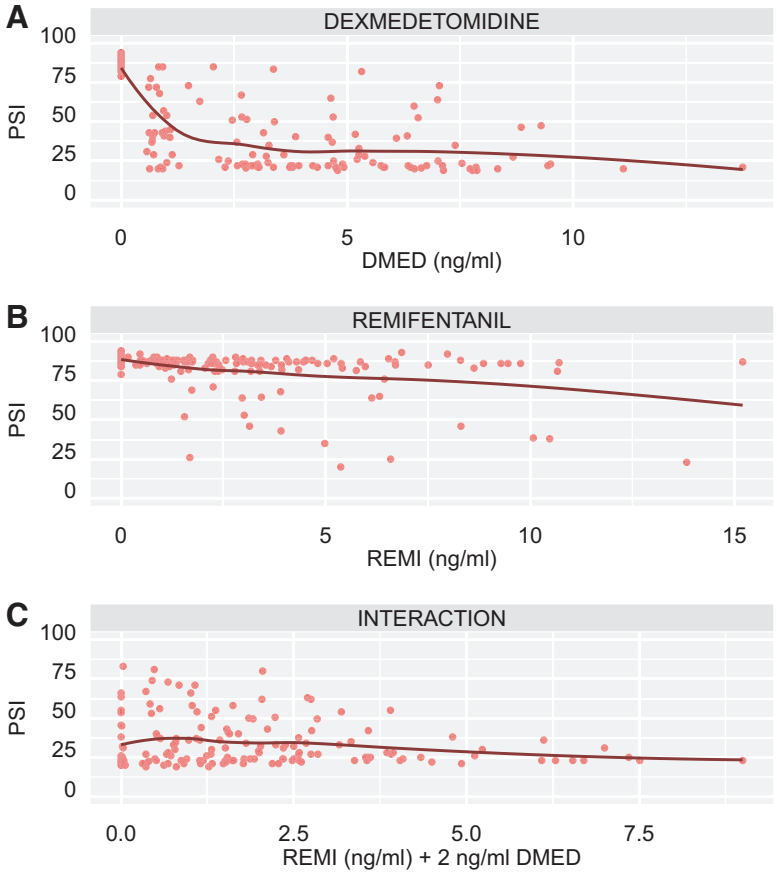

Fig. 3. All observations of the Patient State Index (PSI) obtained during steady-state observation phases plotted *versus* measured plasma concentrations of dexmedetomidine (DMED) and remifentanil (REMI). *Lines* are locally estimated scatterplot smoothers. Remifentanil concentrations are plotted in the interaction phases, with 0 representing a dexmedetomidine background concentration of 2 ng/ml with 0 ng/ml remifentanil.

$kg^{-1} \cdot h^{-1}$ are recommended, resulting in plasma concentrations of less than 2.5 ng/ml.[34] Within this range of dexmedetomidine concentrations, most subjects will appear asleep but remain arousable by name calling or a shake and shout stimulus (figs. 1 and 2). Of the estimated EC50 values for probability of tolerance of the applied stimuli, only the EC50 value (and not EC95) for no response to name called can be reached within clinical accepted concentrations. This is not surprising, because dexmedetomidine is known for its peculiarity that subjects, having fallen asleep, remain arousable within the clinical dose range. Previously it was stated that high concentrations of dexmedetomidine result in deep, unarousable sedation.[3,35] We were surprised that neither addition of remifentanil nor administration of supraclinical concentrations (up to 8 ng/ml) of dexmedetomidine could induce an unarousable state of sedation at a 95% probability of tolerance of laryngoscopy level, which is desirable for anesthetic induction. This study shows that although some volunteers reached an apparent unarousable state (*i.e.*, tolerant of laryngoscopy), a significant proportion of volunteers remained arousable even with high concentrations of dexmedetomidine. Those who did appear unarousable and tolerated a laryngoscopy often also showed some delayed signs of arousal after all observations were done (fig. 5).

Although addition of remifentanil slightly increased the depth of sedation as measured by PSI, it did not increase the probability of no response to name called, tolerance of shake and shout, tolerance of trapezius squeeze, and tolerance of laryngoscopy. Considering the synergistic effect of remifentanil when added to propofol sedation, where remifentanil significantly reduces the concentration of propofol required to reach tolerance of shake and shout and laryngoscopy, our studied drug combination behaves in a very different way.[21] It seems contradictory that remifentanil, a potent analgesic, does not increase the probability of tolerance of trapezius squeeze and laryngoscopy. This can be explained by the fact that those painful stimuli were

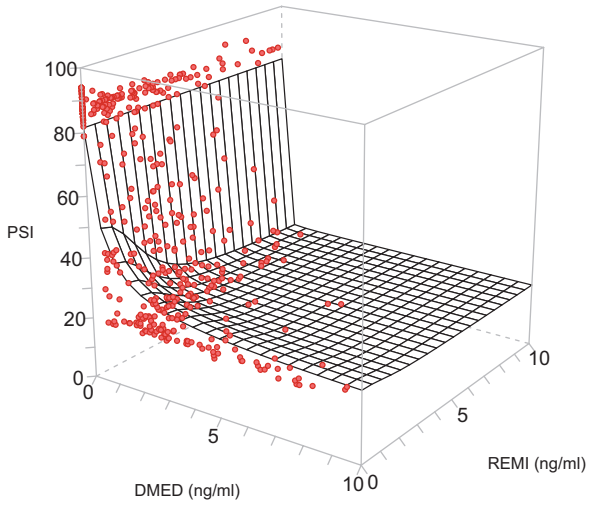

Fig. 4. Response surface for predicted Patient State Index (PSI) *versus* dexmedetomidine (DMED) and remifentanil (REMI) concentrations according to the final model. A window of 0 to 10 ng/ml is shown for both drugs to clarify the view. Observations are plotted as *red dots*.

only applied after no response to name called and shake and shout were tested as incorporated in the MOAA/S assessment. Because dexmedetomidine is known for inducing arousable sedation, subjects might already have been aroused to a certain degree by these preceding nonpainful stimuli before a painful stimulus was applied. Once a sufficient sedation level was reached for assessing tolerance of laryngoscopy, subjects who received remifentanil where less aroused by this painful stimulus, compared with subjects who only received dexmedetomidine (fig. 5). Based on our data, it can be hypothesized that the coadministration of remifentanil during dexmedetomidine infusion, although not influencing the arousability, does decrease the intensity of a laryngoscopy. Earlier work by Kunisawa *et al.*[28] described a markedly lower dexmedetomidine EC50 for tolerance of "awake" laryngoscopy. Possibly subjects remained responsive but also became calm and cooperative. Therefore, although we found no interaction between remifentanil and dexmedetomidine on the pharmacodynamic endpoints tested in this trial, an interaction might be found when one looks at tolerance of awake laryngoscopy.

We found that dexmedetomidine potency increases with advancing age. Older volunteers tolerated noxious stimuli at lower concentrations of dexmedetomidine compared with younger volunteers. Within the clinically recommended dose range, concentrations up to 2.5 ng/ml can be achieved. At a concentration of 2.5 ng/ml, 83% of the 65-yr-old subjects were predicted to reach a sedative state in which they became unresponsive to calling their names. The probability of no response to calling their name for 20-yr-old volunteers at the same concentration is only 36%.

The main side effects observed during and after drug infusions were consistent with previously published adverse events for dexmedetomidine[34] and remifentanil.[36] Ventilatory adverse events (ventilatory depression, bradypnea, apnea) were mainly observed during the remifentanil step-up, whereas hemodynamic adverse events were mainly observed during the dexmedetomidine step-up. As previously shown by Colin *et al.*,[37] hypertension occurs at high dexmedetomidine plasma levels, whereas low plasma

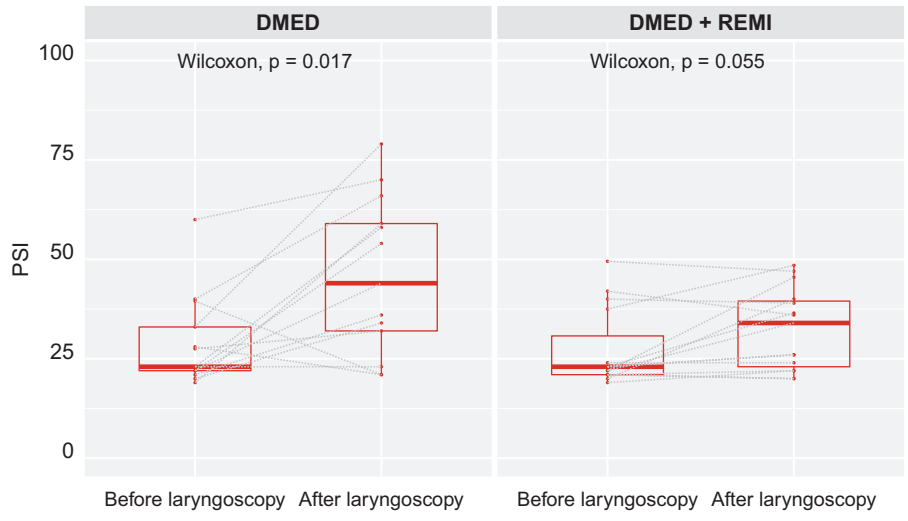

Fig. 5. Patient State Index (PSI) values few minutes before and after subjects tolerated a laryngoscopy, in the dexmedetomidine phase (DMED) and the interaction phase (dexmedetomidine and remifentanil [DMED + REMI]).

concentrations of dexmedetomidine are associated with hypotension. The pharmacokinetic–pharmacodynamic model by Colin *et al.*[37] also shows that because of the slow onset of effects, the slow elimination of dexmedetomidine, and the low EC_{50} for the hypotensive effect, significant hypotension (and orthostatic hypotension) is expected during the recovery period.[37] Based on this, subjects were monitored at least 7 h after cessation of infusion in the dexmedetomidine phase and at least 5 h after the interaction phase. Symptomatic orthostatic hypotension was observed in the recovery period of 8 of 30 dexmedetomidine phases and 6 of 30 interaction phases. Despite our long recovery periods, 9 of the recovery periods needed to be extended because of persistent symptomatic orthostatic hypotension. In clinical practice, these long-lasting hemodynamic side effects are a major limitation for using dexmedetomidine in day care surgery.

We found acceptable performance of the Hannivoort model for dexmedetomidine and the Eleveld model for remifentanil compared with the other available models for these drugs. Median absolute performance errors between 20 and 30% and median performance errors below 20% are considered clinically acceptable and are in line with the performance of current pharmacokinetic–pharmacodynamic models used in target-controlled infusion pumps in anesthesia.[38] Absolute values of the performance criteria as published by Varvel *et al.*[33] have to be carefully interpreted in the context of this study, using supraclinical concentrations of dexmedetomidine and taking into account possible drug interactions. Using much lower concentrations of dexmedetomidine, Obara *et al.*[39] validated the Hannivoort model on their data and found also better performance of the Hannivoort model with a median absolute performance error of 18% and median performance error of 5.6%. When evaluating the performance of the Hannivoort model in the lower (clinical) concentration range, we concluded that no adjustments to the model need to be made for use in clinical practice as long as targets do not exceed 3 ng/ml. Whereas the Eleveld model performed well in the remifentanil phase, a remarkable increase in median performance error and median absolute performance error was seen in the interaction phase. An underlying pharmacokinetic interaction might be present, in which dexmedetomidine reduces remifentanil clearance. To avoid influence of these target-controlled infusion deviations, actual measured plasma concentrations obtained during apparent steady-state observation phases were used for modeling of pharmacodynamic outcomes. Data recorded during wash-out and recovery periods were not used in the modeling process, because during this phase there is no equilibrium between plasma and effect site concentrations.

From the PSI data (fig. 3), it seems that remifentanil alone has a slight effect on the PSI as well. It is not clear whether this reflects a real remifentanil effect or whether it reflects natural relaxation and sleepiness of the volunteers who were placed in supine position in a quiet area, with their eyes closed. The fact that the hierarchical model fitted the PSI data best suggests that the effect of remifentanil on the PSI is negligible. Because assessments of analgesic and sedative endpoints interfere with each other, this study design focused mainly on sedative endpoints. Regarding analgesia, the degree of interaction between remifentanil and dexmedetomidine remains unclear.

In conclusion, low plasma concentrations of dexmedetomidine are required to induce a gradually increasing sedative effect as is measured by PSI (dexmedetomidine EC_{50} = 0.49 ng/ml). However, although they become sedated and appear to be asleep, the majority of subjects remain arousable when stimulated by calling their names, shaking the patient while shouting their names, trapezius squeeze, and laryngoscopy, even when reaching supraclinical dexmedetomidine concentrations. Sensitivity to dexmedetomidine increases with age. Adding remifentanil, although it might reduce the intensity of a painful stimulus, did not alter the arousability of subjects to clinical stimuli. Therefore, although the combination dexmedetomidine and remifentanil might be useful in "conscious sedation" procedures, dexmedetomidine alone cannot be considered suitable to completely replace an intraoperative hypnotic. To ensure deep unarousable sedation as needed for most anesthetic inductions, different (or additional) hypnotics will be required.

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Competing Interests

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