

Dexmedetomidine Pharmacodynamics: Part II

Crossover Comparison of the Analgesic Effect of Dexmedetomidine and Remifentanyl in Healthy Volunteers

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Background: Dexmedetomidine is a highly selective α_2 -adrenoceptor agonist used for short-term sedation of mechanically ventilated patients. The analgesic profile of dexmedetomidine has not been fully characterized in humans.

Methods: This study was designed to compare the analgesic responses of six healthy male volunteers during stepwise target-controlled infusions of remifentanyl and dexmedetomidine. A computer-controlled thermode was used to deliver painful heat stimuli to the volar side of the forearms of the subjects. Six sequential 5-s stimuli (ranging from 41° to 50°C) were delivered in random order. The recorded visual analog scale was used to fit an Emax model.

Results: Compared to baseline, remifentanyl infusions resulted in a right shift of the sigmoid curve (increased T_{50} , the temperature producing a visual analog scale score of 50% of the maximal effect, from 46.1°C at baseline to 48.4° and 49.1°C during remifentanyl infusions) without a change of the steepness of the curve (identical Hill coefficients γ during baseline and remifentanyl). Compared to baseline, dexmedetomidine infusions resulted in both a right shift of the sigmoid curve (increased T_{50} to 47.2°C) and a decrease in the steepness of the curve (decreased γ from 3.24 during baseline and remifentanyl infusions to 2.45 during dexmedetomidine infusions). There was no difference in the pain responses between baseline and after recovery from remifentanyl infusions (identical T_{50} and γ).

Conclusion: As expected, dexmedetomidine is not as effective an analgesic as the opioid remifentanyl. The difference in the quality of the analgesia with remifentanyl may be a reflection of a different mechanism of action or a consequence of the sedative effect of dexmedetomidine.

DEXMEDETOMIDINE is a highly selective α_2 -adrenoceptor agonist used for short-term sedation of mechanically ventilated patients in intensive care units. The combination of its analgesic, sedative/hypnotic, and anxiolytic properties added to its minimal effect on ventilation make dexmedetomidine suitable for use in the perioperative period.¹

The analgesic profile of dexmedetomidine has not been fully characterized in humans.²⁻⁴ This study was designed to further quantify the analgesic effect of dexmedetomidine over a wide plasma concentration range during intravenous infusion. The analgesic effect of opioids is well characterized.⁵ Therefore, to validate our methods and provide a clinical point of reference to the effects measured with dexmedetomidine, we compared the pharmacodynamic effects of dexmedetomidine to remifentanyl, a very short-acting opioid. We measured and compared respiratory, analgesic, and sedative responses of healthy male volunteers during (1) a stepwise target-controlled infusion (TCI) of remifentanyl, (2) a stepwise TCI of dexmedetomidine, and (3) a pseudonatural sleep session. This article focuses on the analgesic effects of dexmedetomidine, whereas a companion article examines the respiratory properties of dexmedetomidine.

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Materials and Methods

Institutional Review Board and Inclusion/Exclusion Criteria

After this study was approved by the Institutional Review Board (Duke University Medical Center, Durham, North Carolina), signed informed consent was obtained from each study subject. Eight male subjects, aged 21-40 yr, with American Society of Anesthesiologists physical status I, were enrolled. Subjects with a history of drug, tobacco, or alcohol abuse; chronic use of medications; gastroesophageal reflux; anticipated difficult airway; body mass index of less than 18 or greater than 28 kg/m²; or the presence of a beard or physiognomies precluding a good fit of a facemask were excluded. The subjects underwent a screening session during which a physical examination, medical history, electrocardiogram, and laboratory tests were performed. During the screening session, the subjects were familiarized extensively with the study procedures. Pain assessments after

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heat stimuli delivered by a computer-controlled thermode were also performed during the screening.

Conduct of the Study

The protocol consisted of three parts, over 24 h. During parts 1 and 2, the subjects received remifentanyl or dexmedetomidine, respectively, *via* TCI. During part 3, no drugs were infused, and no pain data were collected. During parts 1 and 2, the stepwise infusions were designed to target and maintain remifentanyl or dexmedetomidine plasma concentrations at four sequentially increasing steps. Each step lasted 40 min. Steps 1–4 targeted remifentanyl (part 1) plasma concentrations of 1, 2, 3, and 4 ng/ml and dexmedetomidine (part 2) plasma concentrations of 0.6, 1.2, 1.8, and 2.4 ng/ml. Remifentanyl plasma concentrations were chosen (from clinical experience) to be high enough to produce respiratory depression without apnea requiring assisted ventilation, whereas dexmedetomidine plasma concentrations were chosen to range from a therapeutic level to supratherapeutic levels. The first step of dexmedetomidine (0.6 ng/ml) is a typical level used for sedating patients in the surgical intensive care unit. During part 1, at the end of step 4, the remifentanyl infusion was stopped, and a 90-min recovery period was allowed before beginning part 2 to ensure that the subject returned to baseline.⁶ Similarly, the dexmedetomidine infusion was stopped, during part 2 at the end of step 4, and, because the pharmacokinetics of dexmedetomidine is slower than that of remifentanyl, a 240-min recovery period was allowed before beginning part 3.^{7,8}

One of the eight subjects received a placebo instead of remifentanyl, and another subject received a placebo instead of dexmedetomidine. This was randomly assigned, and the investigators were blinded to it. The two placebo subjects were excluded from analysis to perform a crossover comparison.

The subjects fasted for 8 h before the study and were asked to abstain from caffeine and alcohol consumption for the preceding 24 h. On arrival in the morning, an 18-gauge intravenous cannula was inserted, and lactated Ringer's solution was infused at 100 ml/h. A 20-gauge catheter was inserted into the radial artery of the non-dominant hand. The subjects received 30 ml oral sodium citrate, 10 mg intravenous metoclopramide, and 50 mg intravenous ranitidine to minimize the risk of pulmonary aspiration. Electroencephalographic electrodes, a three-lead electrocardiogram, a noninvasive blood pressure cuff, pulse oximeter probes, and Respitrace (Non-Invasive Monitoring Systems Inc., North Bay Village, FL) bands were also applied.

After all the monitors were placed and the facemask was carefully adjusted, the lights were dimmed, and the subject was requested to rest quietly in the bed in the decubitus position for 30–60 min. The protocol was then initiated with baseline measurements.

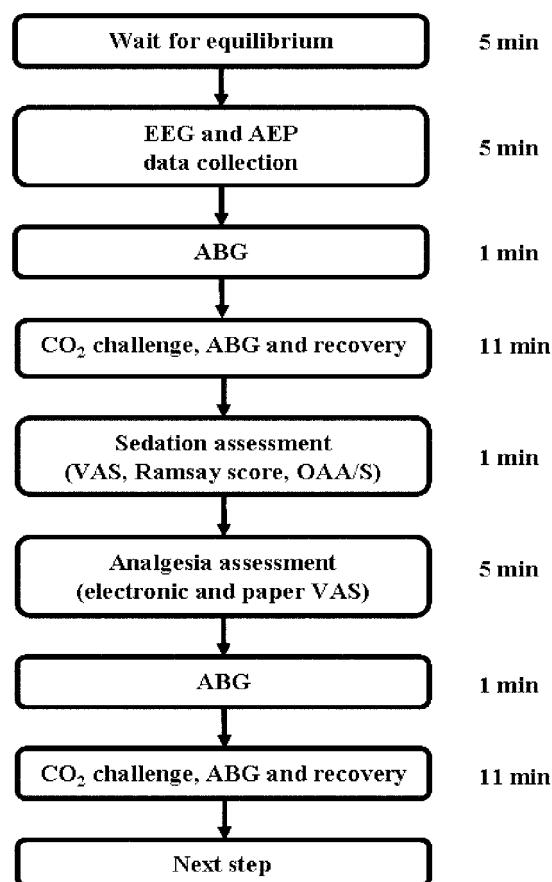


Fig. 1. Sequence of data collection during each 40-min step. ABG = arterial blood gas; AEP = auditory evoked potentials; CO₂ = carbon dioxide; EEG = electroencephalogram; OAA/S = Observer's Assessment of Alertness/Sedation; VAS = visual analog scale.

Measurements

At each step, pharmacodynamic data were collected according to figure 1.⁹ Blood samples were collected for pharmacokinetic analysis at 15–40 min of each step to ensure that a quasi-steady state was achieved.

Heat-pain Stimulation

A 1-cm² computer-controlled Peltier-type thermal stimulator (TSA-II; Medoc Advanced Medical Systems, Minneapolis, MN) was used to deliver painful heat stimuli to the volar side of the forearms of the subjects. Before any stimulus was applied, the subjects were familiarized with the test procedure and were instructed on how to evaluate their pain using both a standard 100-mm-long paper visual analog scale (VAS) that ranged from 0 (no pain) to 100 (worst possible pain) and a computerized VAS box (COVAS; Medoc Advanced Medical Systems) connected to the computer controlling the TSA-II. The subjects then slid a cursor on the control box, indicating the level of pain from 0 (no pain) to 100 (worst possible pain). The position of the cursor was read by the computer. The volar side of both forearms was divided into six zones (fig. 2) and marked with an indelible marker.

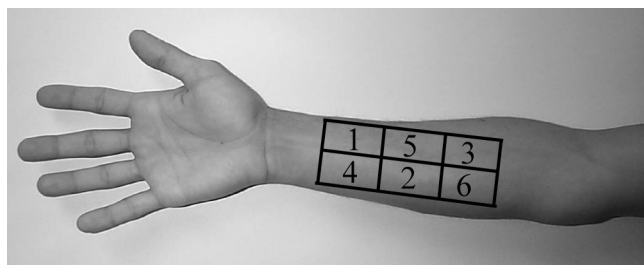


Fig. 2. Volar side of the forearm divided into six zones.

The computer-controlled thermode system was programmed to sequentially deliver one of six different 5-s stimuli of predefined temperatures (41.0°, 42.8°, 44.6°, 46.4°, 48.2°, and 50.0°C). A single probe was used and moved from one zone to another between the stimuli. At each step, the six stimuli were presented in a double-blind and pseudorandom fashion, such that each of the six zones of one forearm received a different stimulus. The right and left forearms were alternatively used from one step to another. During the 25 s between stimuli, the VAS assessments were obtained by one investigator while the probe was repositioned to the following zone by a second investigator. A third investigator (unblinded to the stimuli) operated the computer. The thermode was maintained at 37°C between stimuli. If the painful stimulus was not tolerated, it was stopped, and pain scores were assessed with both methods. If the volunteer was too sedated for pain score assessment, heat stimuli were applied, the VAS and computerized VAS were recorded as “unable to assess,” and withdrawal of the tested forearm was noted as indicated.

Monitoring and Equipment

A customized data acquisition system based on a Lab-View platform (version 6.0; National Instruments, Austin, TX) was used to collect vitals signs, extensive respiratory variables, and the electrocardiogram. The materials and methods of that data collection have been described in detail by Hsu *et al.*⁹

The TCI pump devices consisted of two laptop computers connected to infusion pumps (Harvard Pump 22; Harvard Apparatus, South Natick, MA). STANPUMP** was used to run the TCI pumps. The pharmacokinetic parameters used for the infusions of remifentanil and dexmedetomidine were those published by Minto *et al.*¹⁰ and Dyck *et al.*,⁷ respectively.

Data Analysis

Nonlinear mixed effects models were used to analyze the analgesic effect of dexmedetomidine and remifentanil with S-PLUS (Insightful Corp, Seattle, WA).¹¹ All of

the models were based on the classic sigmoidal Emax model:

$$E = 100 \times \left(\frac{T^\gamma}{T_{50}^\gamma + T^\gamma} \right), \quad (1)$$

where E is the predicted effect (VAS from 0 to 100) for a given temperature (T), T_{50} is the temperature producing 50% of the maximal effect, and γ , the Hill coefficient, is a measure of the steepness of the response.

The model was constrained to temperatures of 37°C or greater with the assumption that the baseline temperature $T = 37^\circ\text{C}$ would result in zero effect $E = 0$. The models were built using the data set collected from six individuals ($i = 1-6$) during eight steps, where steps $j = 1-8$ respectively represent baseline, remifentanil steps 1-4, recovery from remifentanil infusions, and dexmedetomidine steps 1 and 2. During dexmedetomidine steps 3 and 4, the subjects were too sedated to be included in the analysis. Equation 1 was thus rewritten as

$$E_{ij} = 100 \times \left[\frac{(T - 37)^\gamma}{(T_{50,j} - 37)^\gamma + (T - 37)^\gamma} \right] + \epsilon_{ij}, \quad (2)$$

where ϵ_{ij} represents the six residual errors of the i th individual during the j th steps for the six temperatures ($T = 41.0^\circ, 42.8^\circ, 44.6^\circ, 46.4^\circ, 48.2^\circ,$ and 50.0°C).

The initial model (equation 2) included eight γ s and eight T_{50} s (one for each step). The process of model building consisted, in part, of finding which of these 16 parameters were not needed. For example, all of the γ s during remifentanil steps ($\gamma_2, \gamma_3, \gamma_4,$ and γ_5) may be identical and replaced by a single γ_{Remi} .

The quality of the fit was assessed by the values of the Akaike Information Criteria, the magnitude of the standard errors on the parameters estimates, visual examination of the model fit to the raw data, and visual examination of the residual plot.¹¹

Results

Pharmacokinetics and Sedation

While remifentanil target plasma concentrations were 1, 2, 3, and 4 ng/ml, measured plasma concentrations were $0.78 \pm 0.19, 1.70 \pm 0.45, 2.25 \pm 0.52,$ and 3.12 ± 1.28 ng/ml. Dexmedetomidine target plasma concentrations were 0.6, 1.2, 1.8, and 2.4 ng/ml, and measured corresponding plasma concentrations were $0.67 \pm 0.07, 1.72 \pm 0.18, 2.81 \pm 0.20,$ and 3.78 ± 0.36 ng/ml. For both remifentanil and dexmedetomidine, there were no statistical differences between the first and second samples drawn within each step.

Figure 3 shows the sedation assessments measured with the Observer's Assessment of Alertness/Sedation sum.¹² The scale ranges from 9 (completely unresponsive) to 20 (awake and not sedated). The subjects were minimally sedated during remifentanil infusions. During

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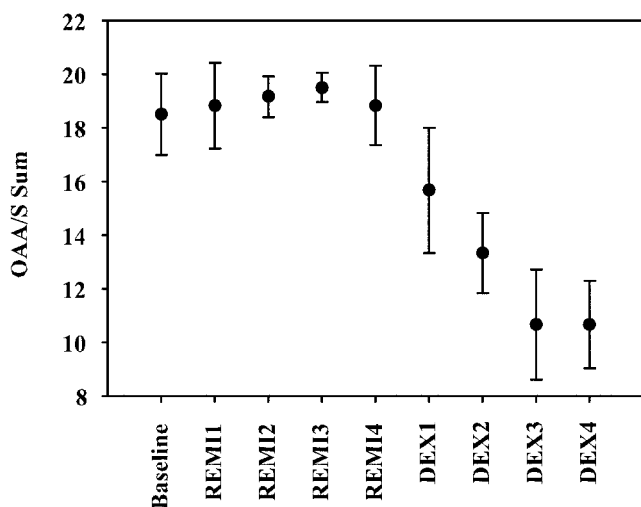


Fig. 3. Observer's Assessment of Alertness/Sedation (OAA/S) sum scores (mean \pm SD) at baseline and at different remifentanyl (REMI) and dexmedetomidine (DEX) steps. The scale ranges from 9 to 20 (maximum sedation to maximum alertness).

dexmedetomidine infusion steps 1 and 2, the subjects were sedated and arousable. In contrast, during steps 3 and 4, deeper levels of hypnosis were attained, and most subjects were completely unarousable (four of the six subjects having received dexmedetomidine).

Pain Model

Because most subjects were completely unarousable during steps 3 and 4 of dexmedetomidine infusions, a VAS score could not be obtained, and no modeling was performed during these steps. However, of the four subjects that were unarousable, three of them consistently withdrew their arm when the higher heat stimuli ($T = 46.4^{\circ}\text{--}50.0^{\circ}\text{C}$) were applied. The model building steps are summarized in table 1, and the parameters of the final model are summarized in table 2. The two pivotal models, model 2 and the final one, model 7, are illustrated in figure 4. There was no difference in the pain response between baseline and recovery from remifentanyl infusions (identical T_{50} and γ). As seen in figure 4, remifentanyl infusions resulted in a right shift of the sigmoid curve (increased T_{50} when compared with

Table 1. Nonlinear Mixed-effect Models

| Model | Fixed Effects | Number of Fixed Effects | AIC | Next Action |
|-------|--|---|----------|---|
| 1 | One γ and one $T_{50}\%$ for each stage | Eight γ s and eight $T_{50}\%$ s | 2349.296 | Considering similarities in their γ s, one γ was used for baseline and recov1, one γ was used for all REMI stages, and one γ was used for the two DEX stages. |
| 2 | One γ for baseline and recovery, one γ for REMI, and one γ for DEX; one $T_{50}\%$ for each stage | Three γ s and eight $T_{50}\%$ s | 2344.955 | Considering that the γ values for baseline-recovery and REMI were similar, only one γ was used for them. |
| 3 | One γ for baseline, recov1, and REMI and one γ for DEX; one $T_{50}\%$ for each stage | Two γ s and eight $T_{50}\%$ s | 2342.965 | Although different γ values were observed between the two γ s, a model with only one γ was further tested. |
| 4 | One γ for baseline, recov1, REMI, and DEX; one $T_{50}\%$ for each stage | One γ and eight $T_{50}\%$ s | 2343.934 | We kept two γ s in our model based on the AIC criteria and the statistical differences between them. The next step was to use the same $T_{50}\%$ for baseline and recov1 based on their similarities. |
| 5 | One γ for baseline, recov1, and REMI and one γ for DEX; one common $T_{50}\%$ for baseline and recov1 | Two γ s and seven $T_{50}\%$ s | 2341.151 | Considering the similarities of the $T_{50}\%$ values for REMI2, 3, and 4, they were modeled with only one $T_{50}\%$. |
| 6 | One γ for baseline, recov1, and REMI, and one γ for DEX; one common $T_{50}\%$ for baseline and recov1 and one common $T_{50}\%$ for REMI2, 3, and 4 | Two γ s and five $T_{50}\%$ s | 2337.283 | Considering the similarities of the $T_{50}\%$ values for DEX1 and 2, they were modeled with only one $T_{50}\%$. |
| 7 | γ for baseline, recov1, and REMI and one γ for DEX; one common $T_{50}\%$ for baseline and recov1; one common $T_{50}\%$ for REMI2, 3, and 4 and one common $T_{50}\%$ for DEX1 and DEX2 | Two γ s and four $T_{50}\%$ s | 2333.294 | We kept this model as our final model. |

AIC = Akaike Information Criteria; DEX = dexmedetomidine; γ = Hill coefficient; recov1 = recovery of remifentanyl infusions; REMI = remifentanyl; $T_{50}\%$ = temperature producing a visual analog scale score of 50%.

Table 2. Final Values of the Fixed Effects with Their Statistical Significance in the Model

| | Mean | SE | P Value |
|-----------------------------------|------|------|----------|
| $\gamma_{\text{Base-Recov-Remi}}$ | 3.24 | 0.23 | < 0.0001 |
| γ_{DEX} | 2.45 | 0.37 | 0.03 |
| $T_{50 \text{ Base-Recov}}$ | 46.1 | 0.49 | < 0.0001 |
| $T_{50 \text{ Remi1}}$ | 48.4 | 0.53 | < 0.0001 |
| $T_{50 \text{ Remi234}}$ | 49.1 | 0.40 | < 0.0001 |
| $T_{50 \text{ Dex}}$ | 47.2 | 0.45 | 0.04 |

$\gamma_{\text{Base-Recov-Remi}}$ = Hill coefficient for baseline, recovery, and remifentanil infusions; γ_{DEX} = Hill coefficient for dexmedetomidine infusions; $T_{50 \text{ Base-Recov}}$ = temperature producing a visual analog scale (VAS) score of 50% during baseline and during recovery from remifentanil infusions; $T_{50 \text{ Dex}}$ = temperature producing a VAS score of 50% during dexmedetomidine infusions; $T_{50 \text{ Remi1}}$ = temperature producing a VAS score of 50% during remifentanil infusion step 1; $T_{50 \text{ Remi234}}$ = temperature producing a VAS score of 50% during remifentanil infusion steps 2, 3, and 4.

baseline), without a change of the steepness of the curve (identical γ s during baseline and remifentanil). Dexmedetomidine infusions resulted in both a right shift of the sigmoid curve (increased T_{50} when compared to baseline) and a decrease in the steepness of the curve (significantly smaller γ during dexmedetomidine when compared with baseline).

Finally, an example of the raw data are found in figure 5.

Discussion

This study, investigating the analgesic effects of dexmedetomidine and remifentanil, adds the following three pieces of information to the current literature. First, a new approach for experimental pain analysis is presented by modeling VAS responses resulting from a wide range (41°–50°C) of heat painful stimuli. Second, the analgesic response of dexmedetomidine is characterized and compared with remifentanil using the experimental heat pain model. Third, we demonstrated a significantly different shape of the pain response during dexmedetomidine infusions when compared with baseline, recovery, and remifentanil infusions.

Approach to Pain Study Analysis

In most experimental pain studies, analgesic effects are modeled using pain threshold, pain tolerance, or both.^{13,14} Hence, only one or two data points of the dose–response curve (intensity of the pain stimuli *vs.* VAS response) are considered. However, in certain conditions, there is a differential drug effect between pain threshold and pain tolerance.¹⁴ In addition, pain threshold has been shown to be increased by pure hypnotic, and pain tolerance is thought to be more reliable in detecting true analgesic effects.¹³

Few investigators have modeled the pain response in function of variable–intensity of the stimulation. Morin and Bushnell¹⁵ modeled the entire stimuli–response but used linear regression. Neugebauer and Li¹⁶ used an approach similar to ours (logistic equation) to model the sigmoid stimulus–response curves in anesthetized rats. Finally,

Eisenach *et al.*¹⁷ used a heat pain experimental method plotting the pain–response as a function of temperature (graph similar to figs. 4 and 5). Although their plot is similar to ours, they only used it at baseline and did not model the stimulus–response.

In contrast, our approach, in human subjects, using an Emax model, analyzed the pain response as a function of variable–intensity stimuli. Although the Emax model has previously been used for pain analysis,^{18–23} these studies modeled dose–responses where the pain–responses are

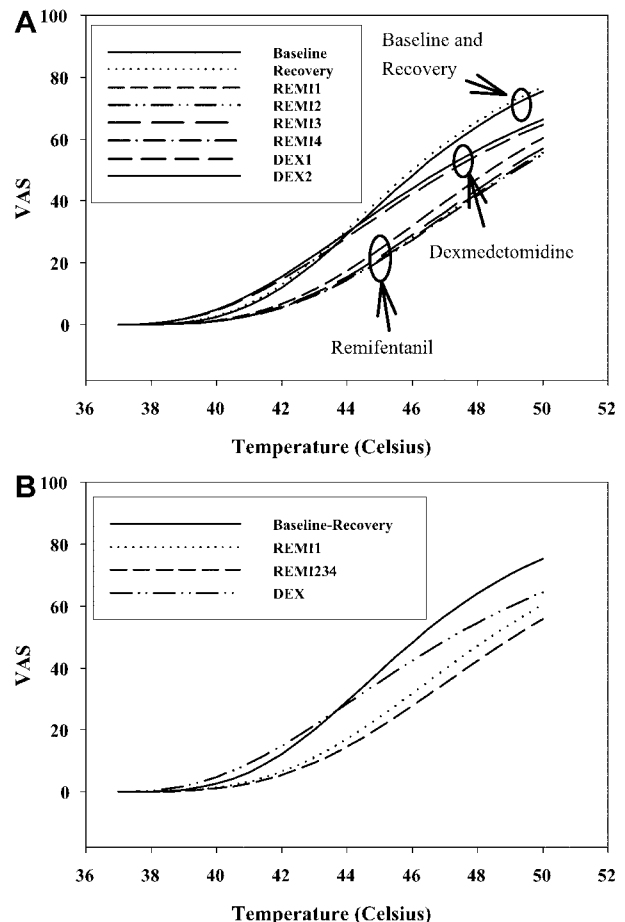


Fig. 4. Population predictions according to model 2 for all the steps (A). This model includes eight T_{50} s, the temperature producing a visual analog scale (VAS) score of 50% of the maximal effect (one for each step), and three Hill coefficients (γ s) (one for baseline and recovery [Baseline–Recovery], one for all remifentanil [REMI] steps, and one for all dexmedetomidine [DEX] steps). The responses are clustered in three groups: Baseline–Recovery, REMI, and DEX infusions. Although not constrained to be identical both, γ s for Baseline–Recovery and REMI turned out to be identical. However, γ for DEX is smaller, resulting in a flatter response during DEX infusions when compared with REMI or Baseline–Recovery. On this model, it can be seen that Baseline and Recovery are identical, as well as DEX1 and DEX2. Although REMI1–4 are clustered and almost identical, it can be seen that REMI1 is apart from REMI2–4. These subjective findings are statistically confirmed, and model 7 (B) was selected as the final model. This model includes four T_{50} s (one for Baseline–Recovery, one for REMI1, one for REMI2–4, and one for DEX1 and 2) and two γ s (one for Baseline–Recovery and REMI, and one for all DEX steps).

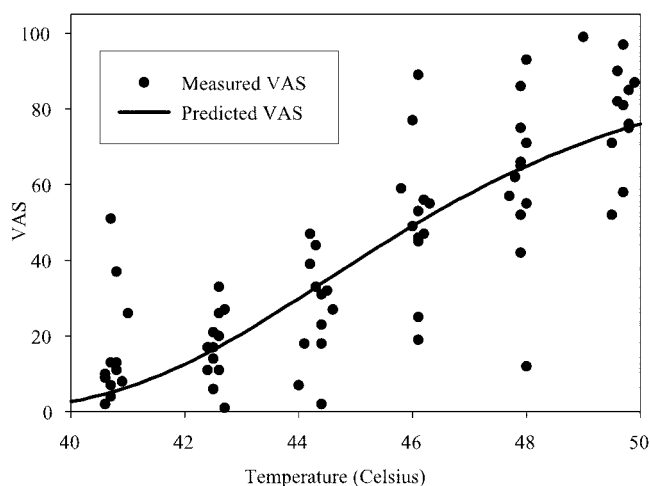


Fig. 5. Population predictions (line) and observed pain response (circles) during baseline and recovery (after remifentanyl, before dexmedetomidine). Both steps are modeled together (same fixed effects) according to our final model. VAS = visual analog scale.

measured for a single-intensity stimulus in function of variable drug concentrations or doses. Rather than examining a single point (e.g., pain threshold or pain tolerance), we have modeled two parameters (T_{50} and γ) that provide not only a measure of the shift of the curve but also its shape. Two different drugs that shift the curve equivalent amount (T_{50}) but with different curve shapes (γ) could suggest different mechanisms of action.

Remifentanyl and Dexmedetomidine Analgesic Effect

In the current study, analgesic effects were documented during both remifentanyl and dexmedetomidine infusions. A drug dose effect was identified with remifentanyl, with an apparent ceiling effect at 2 ng/ml. A ceiling effect (or absence of drug dose effect) was possibly observed with dexmedetomidine since no increase of analgesia was observed by increasing the dose of dexmedetomidine from step 1 to step 2. This impression of a ceiling effect is also supported by the fact that three of the four unarousable subjects consistently withdrew their arm when the higher heat stimuli ($T = 46.4^{\circ}$ – 50.0° C) were applied. In addition, the magnitude of the analgesic effect of dexmedetomidine is smaller than that observed with remifentanyl, which is consistent with the clinical notion that the analgesic property of α_2 agonists is not as effective as that of opioids.

There are little data on the effect of remifentanyl on experimental pain.^{24,25} Gustorff *et al.*²⁵ used the quantitative sensory testing method on the heat pain threshold in volunteers. They derived an E_{50} of $0.05 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ for remifentanyl, which is approximately equivalent to a plasma concentration of 1.2 ng/ml. Although our methodology is different, our results are in accord with their study, because they also observed an apparent ceiling effect at $0.09 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$, which is approx-

imately equivalent to 2 ng/ml. From our clinical perspective, a ceiling effect of an opioid is surprising. This apparent ceiling effect may have resulted from three factors. First, the doses used were relatively small, constrained by the need to maintain spontaneous breathing. Significantly higher doses (resulting in apnea) would likely cause more profound analgesic effects. Second, the current study is likely underpowered to detect subtle changes in analgesia. Finally, although it is controversial,²⁶ the possibility of acute tolerance should be mentioned.²⁷

The observed analgesic effects of dexmedetomidine in this study correlate well with the findings of both animal and human studies. Animal studies have shown significant analgesic effect after systemic administration of clonidine or dexmedetomidine using thermal pain models.^{28,29} Jaakola *et al.*³⁰ evaluated the analgesic effect of systemic administration of dexmedetomidine (0.25, 0.50, and 1 $\mu\text{g}/\text{kg}$) and fentanyl (2 $\mu\text{g}/\text{kg}$) in healthy volunteers, and they demonstrated a moderate analgesic effect of dexmedetomidine with a ceiling effect at 0.5 $\mu\text{g}/\text{kg}$. This is equivalent to our first step of dexmedetomidine infusion (0.6 ng/ml). In contrast, Ebert *et al.*³ used a cold pressor pain model to demonstrate a strong dose-dependent analgesic effect of dexmedetomidine, with no ceiling effect up to plasma concentrations of 8.4 ng/ml. The absence of a ceiling effect in this study may be explained by the use of a different pain model. Another possible explanation is the fact that the painful stimulus of the cold pressor test could be related to peripheral vasoconstriction, whereas dexmedetomidine significantly modulates peripheral vasoconstriction.^{1,31} However, the study of Fuchs *et al.*³² showed that intradermal injection of adrenergic agonists (norepinephrine and phenylephrine) resulted in heat hyperalgesia, whereas injection of nonadrenergic vasoconstrictors (angiotensin II and vasopressin) did not result in heat hyperalgesia, which suggests that adrenergic-mediated mechanisms may play a role in the sensitization of heat nociceptors.

Difference in the Shape of the Stimuli-Response Curves

Another interesting finding of this study is the effect of dexmedetomidine on the shape of the stimuli-dose response. Remifentanyl infusions resulted in an expected increase of T_{50} and an absence of change in the Hill coefficient γ , whereas dexmedetomidine infusions resulted in both an increase in T_{50} and a decrease in the Hill coefficient γ . Potential explanations of the flattened response include the sedative effect of dexmedetomidine and a different mechanism of analgesic action of dexmedetomidine.

It is known that pain perception is decreased when subjects are distracted from the painful stimulus.^{33,34} It has also been proposed that the adrenergic system may be involved in cognitive modulation of pain.³³ The sedative

effect of dexmedetomidine may have resulted in a similar phenomenon.

Limitation of the Study

The pharmacokinetic profile of dexmedetomidine prevented randomization of the sequence of administration of the two drugs, and this is a limitation of the study. Although the development of acute opioid tolerance after remifentanyl infusion is still controversial,^{26,27,35-38} it must be carefully considered because cross-tolerance between opioids and α_2 agonists has been reported.^{39,40} The return of the pain response curve to baseline after recovery from remifentanyl infusions strongly suggests an absence of acute tolerance in our study.

Conclusion

The analgesic effects of both remifentanyl and dexmedetomidine infusions were demonstrated. As expected, the analgesic property of dexmedetomidine was less effective than that of remifentanyl, with the clinical implication that dexmedetomidine could not replace the use of opioids. However, dexmedetomidine exhibited a qualitatively different analgesic effect as shown by a decrease in the pain response slope. The effect of dexmedetomidine on the shape of the analgesic response should be further investigated because it may help to identify the clinical settings in which the analgesic properties of dexmedetomidine can be used most effectively.

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