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Comparative Analgesic and Mental Effects of Increasing Plasma Concentrations of Dexmedetomidine and Alfentanil in Humans

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Background: **In animals, systemic and intrathecal administration of the α_2 -adrenergic receptor agonist dexmedetomidine results in robust antinociceptive effects in models of heat pain. In humans, systemically administered dexmedetomidine is approved for sedating patients in the intensive care unit. However, whether systemic administration of dexmedetomidine in humans produces significant analgesia at doses causing sedation but not unconsciousness remains controversial.**

Methods: **This study in human volunteers used a placebo-controlled, double-blind, and randomized design to examine whether dexmedetomidine at doses causing mild to severe sedation produces analgesia in experimental models of heat and electrical pain. Results were compared to the effects of the μ-opioid receptor agonist alfentanil. A computer-controlled infusion provided four median step-up plasma concentrations of dexmedetomidine (0.09, 0.24, 0.54, and 1.23 ng/ml) and alfentanil (13.4, 33.8, 67.8, and 126.1 ng/ml).**

Results: **Sedative and cognitive effects of dexmedetomidine were dose-dependent, resulting in a median sedation score of 95 of 100 and slowing of cognitive speed (reaction time, trail-making test) by a factor of about two at the highest plasma concentration. Dexmedetomidine did not attenuate heat or electrical pain. Alfentanil caused severe sedation (median sedation score 88 of 100) and slowed cognitive speed by a factor of approximately 1.4 at the highest plasma concentration. Alfentanil attenuated heat and electrical pain dose dependently.**

Conclusion: **This study documents that systemic dexmedetomidine lacks analgesic efficacy for heat and electrical pain at doses causing mild to severe sedation. These results provide further evidence suggesting that systemic administration of dexmedetomidine lacks broad analgesic activity in models of acute pain at doses not rendering humans unconscious.**

DEXMEDETOMIDINE is a specific α_2-adrenergic receptor agonist that possesses both antinociceptive and sedative properties in animals.[1–5] More specifically, studies in animals reported robust antinociceptive effects to noxious heat after systemic or intrathecal administration of dexmedetomidine. In humans, systemic administration of dexmedetomidine has been approved for sedating patients in the intensive care unit. However, experimental human studies exploring the analgesic properties of systemically administered dexmedetomidine provide conflicting results. One group of investigators reported mild to moderate analgesic effects of dexmedetomidine when using the cold pressor test as an experimental model of pain.[6,7] On the contrary, a study conducted in a small number of subjects could not document analgesic activity of dexmedetomidine in a model of cutaneous heat pain or during painful electrical tooth pulp stimulation.[8] These studies administered dexmedetomidine or clonidine at doses producing moderate to severe sedation. The purpose of this study was to further characterize the analgesic properties of dexmedetomidine across a range of plasma concentrations producing mild to severe sedation but not unconsciousness. Models of cutaneous heat and electrical pain were explored because a noxious heat model has proven sensitive in animals for detecting antinociceptive effects of dexmedetomidine, but neither heat nor electrical pain were attenuated by dexmedetomidine in a small number of human volunteers (n = 6).[8] This study also explored the analgesic effects of alfentanil at doses providing a similar degree of sedation as dexmedetomidine to prove sensitivity of examined pain models for detecting analgesic drug action at various levels of sedation and mental impairment.

Materials and Methods

Clinical Protocol

The study was approved by the Institutional Review Board of Stanford University. Twelve healthy subjects (eight men, four women), aged 24 ± 2 yr (mean ± SD) and weighing 74 ± 12 kg (men) and 63 ± 8 kg (women), gave written informed consent. All subjects had a normal physical examination, electrocardiogram, and routine laboratory profile, and a negative drug screen and pregnancy test (women) before enrollment. Subjects did not take any medication except oral contraceptives 4 weeks before and during study participation.

Using a double-blind design subjects were randomly allocated to receive intravenous infusions of dexmedetomidine, alfentanil, and saline placebo. All subjects received all treatments but during different study sessions at least 5 days apart (Latin square randomization). Before participation subjects were familiarized with all tests employed during the study. Timing and the number of tests performed during the training corresponded to that employed during a study session.

Before each study day subjects fasted overnight. On arrival at the study center a catheter was inserted in a

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vein of the left arm for blood drawings. A baseline blood sample was obtained. Another catheter was inserted in a foot vein for drug administration. Monitoring of vital signs was started (electrocardiogram, noninvasive arterial blood pressure, hemoglobin oxygen saturation, and respiratory rate). An intravenous dose of 0.2 mg glycopyrrolate was administered as a precaution to prevent profound bradycardia during drug infusion. Baseline vital signs were recorded 2 min later, followed by baseline pain and mental testing in fixed time order: Experimental heat pain (~5 min), experimental electrical pain (~12 min), trail-making test (~2 min), reaction time (~2 min), and sedation scores (<1 min). These tests are described in more detail below.

Upon completion of baseline testing a computer controlled drug infusion was started aiming at four geometrically increasing (factor 2) target plasma concentrations. Each target concentration was maintained for 45–60 min. While maintaining a target concentration blood for assaying drug plasma concentration was sampled at 15 and 30 min and at the end of each infusion step. Vital signs were recorded at 15 min and at the end of each infusion step. Experimental pain testing followed by mental testing was started 15 min after initiating each infusion step. No testing was performed during the first 15 min of an infusion step to allow drug equilibration between plasma and effect site. It was therefore reasonable to assume that during the actual testing the drug concentration at the effect site was fairly constant and closely related to the measured plasma concentration.

After termination of the drug infusion two subsequent test cycles were performed that were identical in timing and content to those performed during drug infusion. A 15-min interval without testing separated the end of the infusion and the first postinfusion test cycle and the first and second postinfusion test cycle, respectively.

Drug and Drug Infusion

The α_2-adrenergic receptor agonist dexmedetomidine was supplied by Abbott Laboratories (Abbott Park, IL) and the μ-opioid receptor agonist alfentanil was obtained from Janssen Pharmaceutica (Titusville, NJ).

A computer controlled infusion pump (Harvard Pump 22; Harvard Apparatus Inc., South Natick, MA) was used to rapidly achieve and maintain steady state plasma concentrations. Target concentrations increased geometrically and were 0.1, 0.2, 0.4, and 0.8 ng/ml for dexmedetomidine and 20, 40, 80, and 160 ng/ml for alfentanil, respectively. Dexmedetomidine target plasma concentrations were selected to study analgesic effects to experimental pain at concentrations producing mild to severe sedation but not unconsciousness.[7] Alfentanil target plasma concentrations were selected to test the sensitivity of the employed experimental pain model at concentrations providing postoperative pain control and similar levels of sedation as dexmedetomidine.[9] STANPUMP§ was the software driving the pump infusion. The weight-adjusted pharmacokinetic parameters used with STANPUMP are listed in table 1. The person operating the computer-controlled infusion was not blinded to the treatment but did not interact with the study volunteer or the investigator conducting pain and mental tests.

Table 1. Pharmacokinetic Parameters for Computer Controlled Infusion Paradigm

	Dexmedetomidine	Alfentanil
Volume of central compartment (l/kg)	0.7920	0.0312
Micro-rate constant (min^{-1})		
k_{10}	0.0146	0.0910
k_{12}	0.0290	0.0560
k_{13}	–	0.1130
k_{21}	0.0223	0.2140
k_{31}	–	0.0170

Abbott Laboratories (Abbott Park, IL) provided pharmacokinetic parameters for dexmedetomidine; those for alfentanil have been published by Scott and Stanski.[10]

Assay

Five milliliters of venous blood were drawn into heparinized glass tubes, centrifuged, frozen, and stored at −20°C. Dexmedetomidine plasma concentrations were determined by negative ion gas chromatography—mass spectroscopy at Oneida Research Services, Inc. (Whitesboro, New York). Alfentanil plasma concentrations were determined using an electro-spray liquid chromatography tandem mass spectrometry method at Alta Analytical Laboratories, Inc. (El Dorado Hills, CA). The lower limits of quantification were 10 pg/ml for dexmedetomidine and 0.92 ng/ml for alfentanil. The coefficient of variation across a dexmedetomidine concentration range of 50–1500 pg/ml was 4.0–5.4% and across an alfentanil concentration range of 3–345 ng/ml was 3.2–6.0%.

Experimental Pain Test

Nociceptive heat and electrical stimuli were used to test for analgesic effects before, during, and after administration of dexmedetomidine, alfentanil, and saline placebo. The lowest temperature evoking pain (pain threshold) and the highest temperature tolerated (pain tolerance) were determined using a small metal plate in contact with skin. The lowest current evoking pain and the highest current tolerated were determined by constant current administration *via* a skin-surface electrode. Standardized sentences describing the procedure and defining the measured end points were read to subjects before starting an experimental pain test.

Heat Pain Testing. As reported previously, a thermal sensory analyzer (TSA 2001; Medoc Advanced Medical

§ STANPUMP copyright S. L. Shafer, Palo Alto Department of Veterans Affairs Medical Center, Palo Alto, California; software available at http://anesthesia.stanford.edu/. Accessed January 15, 2004.

Systems, Minneapolis, MN) was used to administer the nociceptive heat stimuli.[11] In brief, a hand-held 16 × 16 mm thermode was brought into full contact with skin at the right forearm. After equilibration between skin and thermode temperature at 35°C, the temperature of the thermode was increased by 1°C/s (cutoff at 53°C). Subjects pushed the button of a hand-held device as soon as they felt pain, thereby triggering the recording of the temperature causing pain as well as the immediate cooling of the probe. This procedure was performed three times at sites at least 5 cm apart, and the average of the minimal temperature evoking pain was recorded. Next, using the same algorithm subjects pushed the button of the hand-held device as soon as they were unable to tolerate the evoked pain. The average of the maximum tolerated temperature was recorded. The interstimulus interval was 30 s. If a subject was able to tolerate the maximum output temperature of the device (53°C), this was recorded as the maximum tolerated temperature (16 of 756 recordings).

Electrical Pain Testing. A constant current device (Neurometer; Neurotron Inc., Baltimore, MD) with a maximum output of 20 mA and delivering 5 Hz sine wave pulses of 3-s duration was used to administer nociceptive electrical stimuli. An aluminum/gold electrode was attached to the surface of the skin at the right lateral upper arm as previously described.[11] The interstimulus interval was 15 s.

The test algorithm (slightly modified) and the derivation of the pain threshold and the pain tolerance have been illustrated and described in detail elsewhere.[12] Briefly, a first series of stimuli of increasing intensity was administered to estimate a subject's pain threshold and pain tolerance. If a subject was able to tolerate the maximum output current of the device (20 mA) this was recorded as the maximum tolerated current (six of 252 series). A second series of 10 stimuli of different intensities evenly spaced between the pain threshold and the pain tolerance was administered in random sequence. Subjects rated the magnitude of pain evoked by each stimulus on a 100-mm visual analog scale anchored by the words "no pain" and "most intense pain tolerable." A scatter plot depicting the 10 stimulus intensities (mA) *versus* pain (visual analog scale) resulted. The data were fitted with a linear model ($y = a \times (x - b)$, where x is the current in mA and y is the visual analog scale pain score). The analgesic efficacy variable was the pain threshold determined as the x-intercept and the pain tolerance calculated with aid of the liner model by setting the visual analog scale score to 100.

Mental Testing

Trail-making Test. A modified trail-making test (originally published in German as the "Zahlen-Verbindungs-Test" or "ZVT") was used to assess cognitive speed. The trail-making test is considered a sensitive measure of cognitive performance and correlates significantly with some tests assessing intelligence.[13,14] This paper-and-pencil test consists of four matrices featuring 90 numbers organized in nine rows and 10 columns on a 23 × 21 cm sheet of paper. Subsequent numbers are located in a neighboring row or column. Starting at number 1, a subject has to connect subsequent numbers as quickly as possible. The time to complete the task is recorded. The particular matrix a subject had to complete during a test cycle was chosen randomly.

Reaction Time. The reaction time was measured to assess a subject's alertness and particularly the ability to enhance and sustain reactivity while expecting a high priority signal.[15] This test is considered a sensitive measure of cognitive performance. Subjects were asked to push the key of a hand-held device as quickly as possible when a dot presented on a computer screen changed to a cross. An acoustic signal alerted subjects that the change was imminent. The time interval between the acoustic signal and the change varied randomly. The reaction time was measured 20 times per test cycle and the median was recorded.

Visual Analog Scale Sedation Score. Subjects indicated how sedated they felt by setting a mark on a 100-mm visual analog scale relative to a left and right sided verbal anchor using the wording "not at all" and "as much as possible" (0 = not sedated at all, 100 = sedated as much as possible).

Statistics

Results summarized in tables are expressed as mean and SD if data passed the normality test (Kolmogorov-Smirnov) or alternately as median and interquartile range. However, the SEM, rather than the SD, is represented by error bars to facilitate the reading of graphs.

To determine whether plasma concentrations changed significantly during an infusion step the concentrations measured at 15 and 30 min, and at the end of an infusion step were compared among each other using parametric or nonparametric one-way repeated measures analysis of variance and Student-Newman-Keuls *post hoc* test. As there were four infusion steps, a P value < 0.0125 was considered statistically significant (Bonferroni correction).

To compare analgesic effects, sedative effects, and changes in vital signs among treatments with dexmedetomidine, alfentanil, and saline placebo individual areas under the curves depicting the time *versus* the effect measure were calculated using linear interpolation. Parametric or nonparametric one-way repeated measures analysis of variance and Student-Newman-Keuls test were used to detect significant differences among treatments.

If administration of dexmedetomidine or alfentanil resulted in an effect that was significantly different from that observed for saline placebo, regression analysis was used in pooled data to explore whether a significant plasma concentration *versus* effect relationship existed.

Table 2. Target Plasma Concentrations, Measured Plasma Concentrations and Cumulative Drug Doses During and After Steady-State Infusion of Dexmedetomidine and Alfentanil

	Dexmedetomidine		Alfentanil	
	Plasma concentration (ng/ml)	Cumulative dose (μg)	Plasma concentration (ng/ml)	Cumulative dose (μg)
Infusion step 1	*Target: 0.10*		*Target: 20.0*	
15 min	0.08 ± 0.04	8.9 ± 1.5	11.2 ± 3.6	301 ± 50
30 min	0.09 ± 0.03	11.6 ± 2.0	13.4 ± 3.8	418 ± 70
End	0.10 ± 0.03	14.4 ± 2.6	15.0 ± 4.4*	566 ± 84
Infusion step 2	*Target: 0.20*		*Target: 40.0*	
15 min	0.23 ± 0.07	25.2 ± 4.4	32.9 ± 8.8	919 ± 187
30 min	0.24 ± 0.07	29.6 ± 5.2	35.0 ± 9.1	1121 ± 208
End	0.24 ± 0.07	34.7 ± 6.5	33.8 ± 6.9	1351 ± 222
Infusion step 3	*Target: 0.40*		*Target: 80.0*	
15 min	0.54 ± 0.12	55.7 ± 10.0	67.8 ± 13.8	2107 ± 337
30 min	0.54 ± 0.07	64.4 ± 11.4	68.2 ± 11.4	2491 ± 402
End	0.52 ± 0.12	74.3 ± 13.6	65.7 ± 14.0	3000 ± 520
Infusion step 4	*Target: 0.80*		*Target: 160.0*	
15 min	1.23 ± 0.29	115.6 ± 20.4	124.2 ± 25.4	4465 ± 747
30 min	1.24 ± 0.25	132.7 ± 23.3	126.1 ± 23.2	5233 ± 870
End	1.23 ± 0.17	154.7 ± 29.1	133.2 ± 24.4	6341 ± 1033
Postinfusion 1				
15 min	0.83 ± 0.07	–	102.8 ± 21.7	–
30 min	0.76 ± 0.09	–	82.1 ± 21.5	–
End	0.62 ± 0.05	–	68.8 ± 15.1	–
Postinfusion 2				
15 min	0.62 ± 0.05	–	60.2 ± 16.2	–
30 min	0.49 ± 0.12	–	51.8 ± 16.8	–
End	0.50 ± 0.04	–	44.7 ± 15.9	–

Data are mean ± SD. Target plasma concentrations are indicated in cursive. Plasma concentrations were measured at 15 and 30 min, and the end of each infusion step (infusion steps 1–4). The timing of plasma sampling after stopping the infusion mimicked the timing used during the infusion (postinfusion 1 and 2).

* Plasma concentration of alfentanil increased significantly during infusion step 1. During all other infusion steps the plasma concentration of alfentanil and dexmedetomidine remained constant.

The plasma concentration measured at 15 min after starting each infusion step was used. Plasma concentrations measured during the washout phase of a drug were not considered because equilibration between plasma and effect site could not be assumed precluding the direct correlation of an effect with an actual plasma concentration. Employed pharmacodynamic models were nested in a power model and a maximum likelihood approach was used for parameter estimation. Model equations are not listed in the manuscript because the scope of this study was to determine whether a significant plasma concentration *versus* effect relationship existed for a particular effect measure but not to establish pharmacodynamic models allowing accurate predictions and extrapolations. A P value < 0.05 was considered statistically significant.

Results

Subjects

All 12 subjects completed the investigation according to the protocol. There were no unexpected adverse events. One subject received 0.2 mg glycopyrrolate intravenously for bradycardia (<40 beats/min) during the infusion of dexmedetomidine. Another subject received 10 mg metoclopramide intravenously for severe nausea during the infusion of alfentanil. No other medications (except oral contraceptives and study drug) were administered during study participation.

Drug Infusion

Steady state target plasma concentrations were stable during the infusion steps except for a slight but significant increase of the alfentanil plasma concentration during the first step. Target plasma concentrations, measured plasma concentrations, and cumulative drug doses are listed in table 2. The median coefficient of variation of the steady state plasma concentration was 13% for dexmedetomidine (range, 1 to 55%) and 12% for alfentanil (range, 2 to 77%). The median measured plasma concentration of dexmedetomidine was 13% (range, −100 to 87%) higher than the target concentration. The median measured plasma concentration of alfentanil was 20% lower (range, −84 to 27%) than the target concentration.

Analgesic Effects

Two subjects receiving dexmedetomidine were too sedated to complete experimental pain testing during the fourth infusion and the first postinfusion test cycle.

Heat Pain. Figure 1 (upper graphs) depicts the change of the heat pain threshold and the heat pain tolerance

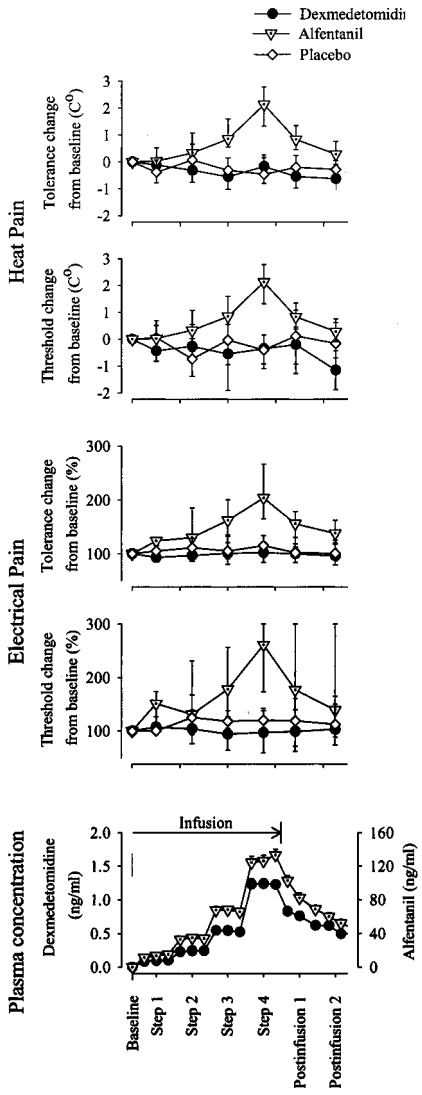

Fig. 1. Pain test results obtained in 12 healthy volunteers before, during (steps 1–4), and after (postinfusion 1–2) a steady state infusion of saline placebo, dexmedetomidine, and alfentanil are depicted as the median and interquartile range. Stable dexmedetomidine and alfentanil plasma concentrations were achieved during four geometrically increasing infusion steps (*bottom graph*). Alfentanil, but not dexmedetomidine, increased the heat and electrical pain threshold and pain tolerance compared with placebo. A significant relationship was detected between the alfentanil plasma concentration and the heat pain tolerance, the electrical pain threshold and the electrical pain tolerance.

from baseline during and after intravenous infusion of dexmedetomidine and alfentanil. Table 3 lists the corresponding values as absolute numbers (°C). Dexmedetomidine was similar to placebo administration and had no analgesic effects irrespective of measured plasma concentration. However, administration of alfentanil resulted in significant analgesia, as indicated by an increased heat pain threshold and heat pain tolerance compared with placebo and dexmedetomidine administration. The increase in pain tolerance, but not pain threshold, was dependent on the plasma concentration. This relationship was linear within the range of plasma concentrations explored in this study. As demonstrated previously, the pain tolerance is more precise than the pain threshold for describing opioid-induced analgesic effects.[11]

Electrical Pain. Figure 1 (middle graphs) depicts the percentage change of the electrical pain threshold and electrical pain tolerance from baseline during and after intravenous infusion of dexmedetomidine and alfentanil. Table 3 lists the corresponding values as absolute numbers (mA). Dexmedetomidine was similar to placebo administration and had no analgesic effects irrespective of measured plasma concentration. However, administration of alfentanil resulted in a plasma concentration dependent increase in pain threshold and pain tolerance that was significantly different form saline placebo (pain tolerance only) and dexmedetomidine administration (pain tolerance and pain threshold). The relationship between the plasma concentration and the effect measures was linear within the range of concentrations explored in this study.

Mental Performance

Trail-making Test. Compared with placebo administration dexmedetomidine and alfentanil decreased the speed of cognitive performance significantly and in a plasma concentration dependent fashion (fig. 2). The relationship between the plasma concentration and the effect measure was linear within the range of concentrations explored in this study. Table 4 lists the corresponding data as absolute numbers. No significant difference was detected between dexmedetomidine and alfentanil administration. At the highest plasma concentration the time to complete the trail-making test was increased by a factor of 2.0 for dexmedetomidine and of 1.4 for alfentanil. Based on data demonstrating a significant correlation between the performance in the trail-making test and the intelligence quotient, the average cognitive speed of our study population corresponded to an intelligence quotient of 122 before drug administration but corresponded to intelligence quotients of 75 and 97 while exposed to the highest dexmedetomidine and alfentanil plasma concentrations.[13]

Reaction Time. Compared with placebo administration dexmedetomidine and alfentanil resulted in a significant and plasma concentration dependent increase of the reaction time (fig. 2). Within the range of plasma concentrations explored in this study, the relationship between the concentration and the effect measure was exponential (exponent > 1) for dexmedetomidine and linear for alfentanil. Table 4 lists the corresponding data as absolute numbers. The reaction time increased significantly more during dexmedetomidine than during alfentanil infusion, *i.e.*, by a factor of 1.8 and 1.4 at the highest plasma concentrations. Based on normative data the average reaction time of our study population corresponded to the 80th percentile before drug infusion but

Table 3. Pain Threshold and Pain Tolerance to Noxious Heat and Electricity Before, During, and After Steady State Infusion of Dexmedetomidine, Alfentanil, and Saline Placebo

	Heat pain (C°)		Electrical pain (mA)	
	Threshold	Tolerance	Threshold	Tolerance
Dexmedetomidine				
Preinfusion	44.6 (43.2–46.2)	48.9 (48.3–49.5)	1.7 (1.1–2.2)	6.9 (6.1–8.0)
Infusion step 1	45.0 (42.7–46.3)	48.5 (48.1–49.9)	1.6 (1.2–2.4)	6.0 (5.5–7.5)
Infusion step 2	44.0 (43.0–45.7)	48.7 (48.1–49.2)	1.9 (1.1–2.4)	6.3 (5.0–7.9)
Infusion step 3	44.0 (42.3–46.5)	48.4 (47.9–48.8)	1.6 (1.2–2.0)	6.5 (4.9–7.9)
Infusion step 4	44.0 (42.7–45.6)	48.8 (47.8–49.7)	1.5 (0.8–2.5)	6.7 (5.2–8.5)
Postinfusion 1	44.1 (43.7–45.2)	48.3 (47.9–49.1)	1.6 (0.9–2.3)	6.3 (5.0–7.9)
Postinfusion 2	43.9 (42.0–45.2)	48.2 (47.9–49.2)	1.5 (1.0–3.1)	5.8 (4.9–8.3)
Alfentanil				
Preinfusion	43.8 (43.1–45.3)	49.1 (48.4–49.5)	1.1 (0.6–1.3)	5.7 (4.4–6.4)
Infusion step 1	45.5 (43.8–45.9)	49.0 (48.3–50.1)	1.7 (1.1–2.0)	6.8 (5.5–8.7)
Infusion step 2	44.8 (44.5–45.8)	48.9 (48.5–50.6)	1.7 (1.2–1.9)	8.2 (7.3–9.7)
Infusion step 3	45.6 (44.6–46.1)	49.9 (48.9–51.1)	1.6 (1.1–2.1)	9.8 (8.4–11.8)
Infusion step 4	46.1 (44.5–46.5)	51.5 (49.6–52.3)	1.9 (1.6–3.3)	12.4 (10.6–12.7)
Postinfusion 1	45.3 (44.3–46.1)	49.6 (48.8–51.4)	1.6 (1.1–2.3)	8.5 (7.1–10.3)
Postinfusion 2	44.9 (44.2–45.7)	49.3 (48.6–50.6)	1.7 (1.2–2.2)	8.4 (6.0–10.1)
Saline placebo				
Preinfusion	44.8 (43.9–45.6)	48.6 (47.9–49.9)	1.6 (1.3–2.4)	6.5 (5.1–8.0)
Infusion step 1	44.3 (43.4–46.3)	48.3 (47.5–49.5)	1.8 (1.4–2.5)	7.3 (5.9–8.2)
Infusion step 2	44.5 (42.9–45.9)	48.3 (47.9–49.9)	2.1 (1.6–3.0)	7.8 (6.4–9.0)
Infusion step 3	44.1 (42.8–46.4)	48.2 (47.4–49.7)	2.1 (1.6–2.8)	7.6 (6.3–8.9)
Infusion step 4	44.1 (42.9–45.8)	48.1 (47.2–49.4)	2.1 (1.7–3.2)	7.5 (6.2–10.2)
Postinfusion 1	44.8 (42.8–46.3)	48.4 (47.6–49.4)	2.0 (1.5–3.1)	7.3 (5.9–9.5)
Postinfusion 2	44.1 (43.1–46.1)	48.4 (47.4–49.3)	2.4 (1.4–3.1)	7.5 (6.3–9.2)

Data are median and interquartile range. Results were obtained before starting the drug infusion (preinfusion), during the steady state infusion targeting four geometrically increasing plasma concentrations (infusion steps 1–4), and twice after stopping the infusion (postinfusion 1 and 2). Alfentanil administration increased the pain threshold and pain tolerance to noxious heat and electricity compared with saline placebo and dexmedetomidine administration. There was no difference between dexmedetomidine and saline placebo administration. Alfentanil administration increased the heat pain tolerance and the electrical pain threshold and pain tolerance in a plasma concentration dependent fashion.

dropped down to the 2nd and 10th percentiles while subjects were exposed to the highest plasma concentrations of dexmedetomidine and alfentanil.[15]

Sedation Score. Compared with placebo administration dexmedetomidine and alfentanil increased the sedation score significantly and in a plasma concentration dependent fashion (fig. 2). Within the range of plasma concentrations explored in this study, the relationship between the concentration and the effect measure was exponential (exponent < 1) for dexmedetomidine and linear for alfentanil. Table 4 lists the corresponding data as absolute numbers. No significant difference was detected between dexmedetomidine and alfentanil administration. Sedation scores tended to be higher during dexmedetomidine infusion and subjects indicated to be almost maximally sedated at the highest plasma concentration. Sedation scores before administering dexmedetomidine, alfentanil, and placebo ranged between 22 and 28, indicating that a portion of the overall sedation score was not related to drug administration.

Vital Signs

Infusion of dexmedetomidine resulted in a significant decrease of systolic and diastolic blood pressures and heart rate as compared with alfentanil and saline placebo (fig. 3). The relationship between the plasma concentration and the three effect measures was exponential (exponent <1) within the range of concentrations explored in this study. No difference was detected between alfentanil and saline placebo administration.

Infusion of alfentanil resulted in a significant decrease of respiratory rate and hemoglobin oxygen saturation as compared with dexmedetomidine and saline placebo (fig. 3). The relationship between the plasma concentration and the two effect measures was linear within the range of concentrations explored in this study. No difference was detected between dexmedetomidine and saline placebo administration.

Discussion

The aim of this study in human volunteers was to determine whether systemic administration of the α_2-adrenergic receptor agonist dexmedetomidine attenuates experimentally induced heat and electrical pain at plasma concentrations, resulting in mild to severe sedation. We report that intravenous administration of dexmedetomidine lacked analgesic efficacy, even at plasma concentrations causing severe sedation and impairment of cognitive speed.

Systemic administration of the α_2-adrenergic receptor

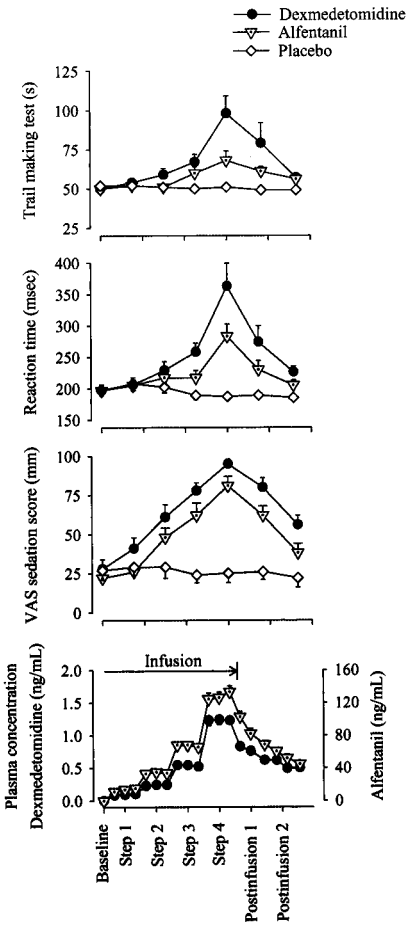

Fig. 2. Mental test results obtained in 12 healthy volunteers before, during (steps 1–4), and after (postinfusion 1–2) a steady state infusion of saline placebo, dexmedetomidine, and alfentanil are depicted as the mean and SEM. Dexmedetomidine and alfentanil significantly increased the time needed to complete the trail-making test, the reaction time, and the subjective visual analog sedation score compared with placebo. Dexmedetomidine increased the reaction time significantly more than alfentanil, but no differences were detected between the two drugs for the trail-making test and the subjective visual analog sedation score. A significant relationship was detected for both drugs between the plasma concentration and the trail-making test, the reaction time, and the subjective visual analog sedation score.

Table 4. Trail-making Test, Reaction Time, and Visual Analog Sedation Score Before, During, and After Steady State Infusion of Dexmedetomidine, Alfentanil, and Saline Placebo

	Trail making test (s)	Reaction time (ms)	Sedation score (VAS)
Dexmedetomidine			
Preinfusion	50 ± 7	197 ± 22	28 ± 21
Infusion step 1	54 ± 8	206 ± 28	41 ± 24
Infusion step 2	59 ± 12	229 ± 48	61 ± 27
Infusion step 3	67 ± 17	258 ± 50	78 ± 18
Infusion step 4	105 ± 51	363 ± 126	95 ± 10
Postinfusion 1	79 ± 46	274 ± 88	80 ± 19
Postinfusion 2	57 ± 6	226 ± 32	56 ± 22
Alfentanil			
Preinfusion	50 ± 8	197 ± 32	22 ± 20
Infusion step 1	52 ± 8	205 ± 43	26 ± 15
Infusion step 2	51 ± 5	217 ± 43	48 ± 22
Infusion step 3	60 ± 13	217 ± 41	62 ± 27
Infusion step 4	68 ± 19	283 ± 67	81 ± 22
Postinfusion 1	61 ± 10	230 ± 49	62 ± 21
Postinfusion 2	56 ± 8	205 ± 28	38 ± 20
Saline placebo			
Preinfusion	52 ± 8	197 ± 26	27 ± 21
Infusion step 1	52 ± 8	208 ± 38	29 ± 19
Infusion step 2	51 ± 7	202 ± 30	29 ± 23
Infusion step 3	50 ± 7	189 ± 23	24 ± 18
Infusion step 4	51 ± 7	187 ± 17	25 ± 22
Postinfusion 1	49 ± 7	189 ± 17	26 ± 17
Postinfusion 2	49 ± 7	185 ± 13	22 ± 22

Data are mean ± SD. Results were obtained before starting the drug infusion (preinfusion), during the steady state infusion targeting four geometrically increasing plasma concentrations (infusion steps 1–4), and twice after stopping the infusion (postinfusion 1 and 2). Dexmedetomidine and alfentanil administration increased the time to complete the trail making test, the reaction time, and the visual analog subjective sedation scores significantly and in a dose-dependent fashion compared with saline placebo. Dexmedetomidine increased the reaction time significantly more than alfentanil, but no differences were detected between the two drugs for the trail making test and the subjective visual analog sedation score.

agonists dexmedetomidine and clonidine has been reported to produce sedative and opioid-sparing effects in the perioperative setting, providing indirect evidence for some analgesic efficacy.[16–20] However, studies conducted in the perioperative setting are subjected to confounding factors and it is difficult to distinguish between analgesic and sedative effects as a cause for observed opioid-sparing effects.

Experimental pain studies in human volunteers using the cold pressor test documented a 20–30% decrease of the visual analog pain score in subjects receiving dexmedetomidine or clonidine at doses causing moderate to severe sedation.[6,7,21] In contrast, a study performed with experimental heat pain and electrical tooth pulp stimulation failed to detect any analgesic effect while reporting a significant attenuation of the unpleasantness, but not of the intensity, of pain in a model of ischemic pain after administration of the $\alpha_2$adrenergic receptor agonist medetomidine at a dose producing severe sedation.[8] Finally, volunteers exposed to clonidine at a dose producing moderate to severe sedation did not experience any antihyperalgesic or antiallodynic effect in an experimental model of secondary hyperalgesia.[22] Our results add to the evidence suggesting that dexmedetomidine lacks broad analgesic efficacy after systemic administration of doses producing mild to severe sedation.

Experimental pain may not predict whether a systemic dose of dexmedetomidine can alleviate clinical pain. For example, systemic administration of medetomidine attenuates the unpleasantness, but not the intensity, of ischemic pain.[8] Reducing the unpleasantness of pain may be relevant in the treatment of clinical pain. Similarly, dexmedetomidine interacts synergistically with endogenous mechanisms underlying stress-induced analgesia and therefore may have a role as an analgesic compound for clinical pain associated with high levels of stress.[23]

However, there is robust evidence that the α_2 agonist

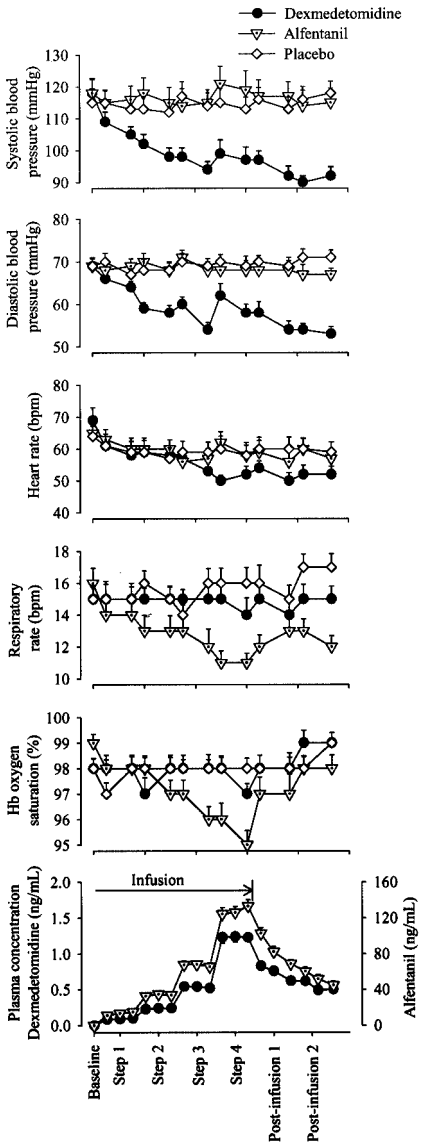

Fig. 3. Vital signs recorded in 12 healthy volunteers before, during (steps 1–4), and after (postinfusion 1–2) a steady state infusion of saline placebo, dexmedetomidine, and alfentanil are depicted as the mean and the SEM. Dexmedetomidine decreased the systolic and diastolic blood pressures and the heart rate significantly and in plasma concentration dependent fashion compared with saline placebo and alfentanil. There was no difference detected between saline placebo and alfentanil. Alfentanil decreased the respiratory rate and the hemoglobin oxygen saturation significantly and in plasma concentration dependent fashion compared with saline placebo and dexmedetomidine. There was no difference detected between saline placebo and dexmedetomidine.

clonidine administered *via* the intrathecal or epidural route produces significant analgesia in postoperative pain and in cancer pain states, for the latter particularly if neuropathic in origin.[24–26] Interestingly, experimental pain models that failed to detect an analgesic effect of a α_2 agonist after its systemic administration, readily detect such an effect after its intrathecal or epidural administration.[27] Parallel documentation of analgesic efficacy in models of clinical and experimental pain for the intrathecal and epidural route, and lack thereof for the intravenous route, casts further doubt on whether systemic administration of a α_2 -agonist will provide a robust analgesic effect for a variety of clinical pain states. This does not preclude the possibility that systemic administration of a α_2 agonist could be useful for some types of clinical pain or may be a valuable therapeutic adjuvant acting synergistically to enhance the analgesic action of another pain therapeutic.

Animal data show a dose-dependent response for both antinociception and sedation with systemic administration of a α_2 agonist.[28,29] Human data show a clear dose-response relationship for sedation, but not for analgesia, with systemic administration of a α_2 agonist.[8,30,31] Findings between animal and human studies may be divergent because animal studies used doses that were several orders of magnitude larger than those used in human trials.[18,28–30] Human studies may not allow using an effective analgesic dose of a α_2 agonist *via* the systemic route because such a dose may render subjects heavily sedated or even unconscious. Administration of a α_2 agonists *via* the intrathecal or epidural route likely spares supraspinal central nervous system sites from extensive drug exposure, thereby providing robust analgesic effects in most subjects without producing severe sedation.[28,30]

Despite profound sedation and substantial impairment of cognitive speed at high plasma concentrations of dexmedetomidine and alfentanil, dexmedetomidine exerted no analgesic action, while alfentanil resulted in a robust analgesic effect. Contrariwise, significant analgesic effects of alfentanil were documented at low plasma concentrations that did not produce profound sedation or mental impairment. This study illustrates that sedative and analgesic drug effects could clearly be distinguished, *i.e.*, did not confound each other.

Dexmedetomidine decreased heart rate and blood pressure in dose-dependent fashion. These cardiovascular effects of dexmedetomidine are well documented for the explored plasma concentrations.[7] However, at higher plasma concentrations dexmedetomidine increases blood pressure while heart rate is further decreased.[7] Dexmedetomidine did not affect respiratory rate or hemoglobin oxygen saturation. This is consistent with previous data suggesting that ventilation is only mildly affected at plasma concentrations up to 10 times higher than the peak concentrations reported here.[7] However, if dexmedetomidine is administered intravenously as a bolus (1–2 μg/kg in 2 min) the ventilatory pattern can become irregular and short episodes of apnea have been described.[5]

In summary, this study provides further evidence in human volunteers that systemically administered dexmedetomidine lacks broad analgesic activity in models of acute pain at plasma concentrations producing mild to severe sedation but not unconsciousness.

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