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Effects of Intravenous Dexmedetomidine in Humans

I. Sedation, Ventilation, and Metabolic Rate

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Dexmedetomidine (DMED) is a highly selective centrally acting α_2-adrenergic agonist thought to provide significant sedation without appreciable ventilatory effects. This double-blind, placebo-controlled experiment evaluated four dose levels of DMED (0.25, 0.5, 1.0, and 2.0 μg/kg intravenously over 2 min) in 37 healthy male volunteers. Measurements of sedation, arterial blood gases, resting ventilation, hypercapnic ventilatory response (HVR), and metabolic rate (O_2 consumption and CO_2 production) were performed at baseline, 10 min after DMED infusion, and thereafter at the end of each subsequent 45-min period. DMED caused sedation resulting in loss of responsiveness in most of the subjects administered 1.0 and 2.0 μg/kg; sedation was evident for 195 min following 2.0 μg/kg ($P < .05$). Ten minutes following infusion of 1.0 and 2.0 μg/kg, Pa_{CO_2} had increased by 5.0 and 4.2 mmHg, respectively ($P < .05$), and 60 min following 2.0 μg/kg, $\dot{V}_E$ had decreased by 28% ($P < .05$). The placebo group showed a progressive increase in the HVR slope (50% increase by 330 min following the infusion; $P < .05$). Overall, across all the DMED doses, the slope was decreased ($P < .05$) at all times after DMED. The calculated ventilation at a Pa_{CO_2} of 55 mmHg was decreased (39%; $P < .05$) 10 min following 1.0 and 2.0 μg/kg, returning to control values by 285 min following 2.0 μg/kg. O_2 consumption increased 16% ($P < .05$) at 10 min following 2.0 μg/kg; CO_2 production decreased (22% at 60 min). By 5 h postinfusion, both had returned to normal. Intravenous DMED caused sedation and sleep with minor decreases in resting ventilation, whereas the HVR was reduced slightly. The increase in oxygen consumption seen immediately after administration of DMED is not readily explained by the known physiologic effects of α_2-adrenergic agonists. (Key words: Metabolism: glucose. Sympathetic nervous system, α_2-adrenergic agonist: dexmedetomidine. Ventilation: hypercapnic ventilatory response.)

RELIEF OF PAIN without associated ventilatory depression remains an elusive goal. While we are being encouraged to eliminate pain in the postoperative surgical patient (*cf* Louis Sullivan, DHSS) the morbidity associated with hypercapnia and hypoxia, especially in the immediate postoperative period, necessitates close monitoring of patients administered opioid analgesics. Recently, the α_2-adrenergic receptor agonist dexmedetomidine has been shown to provide analgesia in humans,[1] whereas in dogs it only caused relatively mild ventilatory depression.[2] However, case reports of accidental extreme overdose of clonidine and other α_2 agonists indicate respiratory depression may develop[3–6] although it is difficult to assess the degree of ventilatory depression because of the paucity of data. Some clinical studies have suggested clonidine to have no or only minimal respiratory depression,[7,8] whereas others have shown a decreased response to CO_2 when clonidine is given orally‖ or epidurally.[9] Episodes of decreased hemoglobin oxygen saturation have also occurred following oral clonidine.[10]

In clinical practice, clonidine and, more recently, the highly selective α_2 agonist dexmedetomidine (DMED) have been used in the perioperative period to provide sedation,[11,12] analgesia,[8,13,14] and anxiolysis;[11] to reduce opioid, thiopental, and inhalation anesthetic requirements;[11,12,15–19] and to reduce hemodynamic instability.[12,18,19] Yet the ubiquitous distribution of α_2 receptors throughout the central nervous system and periphery introduces the potential for unwanted side effects even from highly receptor-selective drugs, such as DMED.

This study was designed to determine the sedative, ventilatory, and metabolic effects of DMED in healthy male volunteers. The hemodynamic effects of DMED were also measured and are reported in an accompanying paper.[20]

Methods

SUBJECTS

This double-blind, placebo-controlled study was approved by the UCLA Human Subject Protection Committee and all subjects gave written informed consent. Thirty-seven normal, healthy male volunteers between the ages of 18 and 45 years, weighing less than 100 kg, participated in this study. Each subject was free of signif-

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‖ Rouge P, Dureuil B, Loiseau A, Desmonts JM: Effects of clonidine on the ventilatory response to CO2 (abstract). ANESTHESIOLOGY 71: A1090, 1989.

icant cardiac or respiratory disease and had normal serum chemistry, liver function tests, CBC, urinalysis, and ECG prior to the study. If there was any evidence of acute or chronic disease, drug use, or routine use of medications, the volunteer was excluded from the study.

Dexmedetomidine was administered intravenously at four dose levels. All the subjects in a given dose group were studied before proceeding to the next higher dose. Placebo-treated subjects were randomly interspersed within each dose group. In each of the 0.25, 0.5, and 1.0 μg/kg dose groups, 6 subjects received DMED and 2 received placebo. In the 2.0 μg/kg dose group, 10 subjects received DMED and 3 received placebo. Thus, there was a total of 37 subjects studied, of which 9 received placebo. Each subject participated in only one experiment.

All subjects arrived at the laboratory at 8 AM after an overnight fast and having refrained from alcohol, coffee, tea, and other drugs for at least 24 h. Each subject was studied while in a semirecumbent position with an arterial catheter in place through which all blood samples were drawn into a heparinized plastic syringe over 15–30 s after removal of an appropriate sized aliquot to clear the deadspace. Patency of the catheter was maintained with heparinized saline (0.5 U/ml). Lead II ECG (Siemens 404-1, Danforth, MA), pulse oximetry measured hemoglobin oxygen saturation by ear probe (Sp_{O_2}; Ohmeda 3700, fast averaging mode), chest and abdominal excursion was measured using respiratory inductive plethysmography (Respitrace, AMI, Ardsley, NY), and ear canal (tympanic) temperature (Yellow Springs Instruments, Yellow Springs, OH) were monitored continuously. Intravenous normal saline was given at an appropriate maintenance rate throughout the study; in addition, during the first hour, one-half of the calculated volume deficit was replaced. The subjects were allowed to rest for at least 1 h following instrumentation.

Measurements

Two baseline measurements were taken at 90 and 45 min prior to the infusion of the drug or placebo. The baseline values reported for all measurements are the averages of these two measurements. The test drug was infused by syringe pump (Harvard Apparatus, Billerica, MA) over 2 min. Ten minutes after the beginning of infusion, the first set of post-treatment measurements were made and these were repeated at 60- and 45-min intervals thereafter. At each period sedation, ventilation, arterial blood gases, oxygen consumption and carbon dioxide production were measured as described below.

Sedation / Anxiety

Subjects used a visual analog scale (VAS) to rate their states of sedation (1 = fully alert and 10 = asleep) and anxiety (0 = no anxiety and 10 = most severe anxiety imaginable). If, at the time the VAS scores were to be recorded, the subject was asleep and could not be awakened by voice command, a score of 100 was recorded for sedation and a score of zero was recorded for anxiety.

Ventilation

During the ventilatory measurements the subjects listened to music of their choice, wore a noseclip and breathed through a mouthpiece from a gas mixing chamber in which the O_2 and CO_2 concentrations could be adjusted on a breath-by-breath basis. The inspired concentrations of O_2 and CO_2 were manipulated by a computer-controlled combination of feedback and open-loop control to precisely control the end-tidal gas tensions on a breath-by-breath basis. Ventilation was measured using a impeller flowmeter (VMM-110, Sensor Medics, Laguna Hills, CA) and oxygen and carbon dioxide concentrations at the mouth were measured with a mass spectrometer (Perkin Elmer MGA 1100). The impeller flowmeter was calibrated by a motorized piston pump with a 1-l tidal volume (SAL-30, Alpha Technologies, Laguna Hills, CA). The mass spectrometer was calibrated with two concentrations of standard calibration gases for each gas species measured.

During the first 5 min, subjects breathed reconstituted room air to obtain resting ventilation data. This room air was reconstituted with oxygen and nitrogen flows in the chamber and because of technical considerations the FI_{O_2} was approximately 22% (constant throughout an individual experimental day). This was followed by a 5-min "run-in period" in which the subject breathed 55% O_2 and varying amounts of CO_2 to maintain the PET_{CO_2} at 45 mmHg. After the run-in period a hypercapnic response (pseudo-rebreathing) was performed increasing the PET_{CO_2} from 45 to 65 mmHg over 5 min in a background of 55% O_2. Between measurement periods the subjects rested, breathing room air without the mouthpiece.

Data were collected on a breath-by-breath basis and stored by computer. The division of the flow signal into inspired and expired volumes and times was done by software[21] and ventilation was converted to BTPS. The resting minute ventilation was derived by averaging the data obtained during the 5-min period breathing room air. The hypercapnic response was calculated by fitting a straight line to the breath-by-breath ventilation *versus* PET_{CO_2} data using least squares regression and reported as the slope and the intercept at PET_{CO_2} = 55 mmHg.

Metabolic Rate

Oxygen consumption and carbon dioxide production were measured and corrected to STPD on a breath-by-breath basis.[21] The analog signals from the flowmeter and

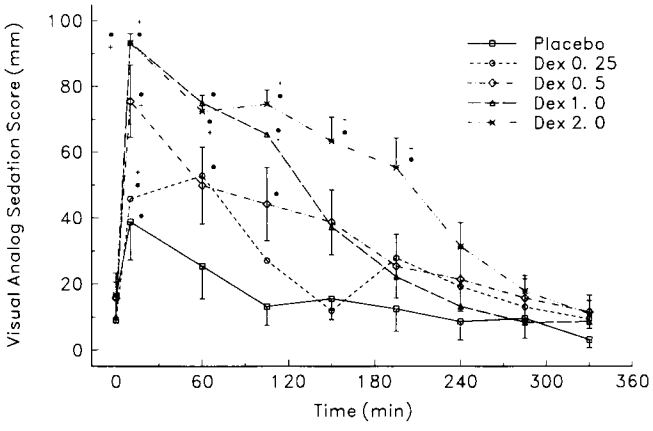

FIG. 1. Average sedation VAS for the four dose groups and placebo. For clarity SEM is shown for the placebo and 0.5 and 1.0 μg/kg groups. Time 0 is the average of the two pre-infusion baseline measurements. The first postdrug measurements were made at 10 min after the drug infusion. *$P < .05$ different from the baseline (time = 0) measurement within a dose group. +$P < .05$ different from the placebo group measurement at the same time point.

mass spectrometer were sampled at a 50-Hz rate by the computer and the oxygen consumption and carbon dioxide production were calculated with software[21] using the difference between the inspired and expired gas volumes after correcting for nitrogen balance and changes in lung volume.[22] The breath-by-breath values were then averaged over at least a 1-min period of stable ventilation.

Blood Samples

The arterial blood samples were drawn just prior to the start of the hypercapnic test and were immediately placed on ice and analyzed for glucose (Beckman Synchron Clinical System CX3, Fullerton, CA) and blood gases (Instrumentation Laboratories 1303, Lexington, MA).

Statistical Analysis

Statistical analysis for the comparability of pooled placebo, 0.25, 0.5, 1.0, and 2.0 μg/kg dose groups with regard to age, weight and height, was examined using a one-way general linear model analysis of variance for unbalanced parallel designs. Treatment group comparability with regard to racial distribution, baseline physical exam, medical history, and substance consumption (nicotine, caffeine, alcohol) was performed using the likelihood ratio statistic. Statistical analysis of the measurement data was performed by two-way ANOVA with *post hoc* Newman-Keuls tests (Solo, BMDP, Los Angeles, CA). Comparisons within a dose group were made to the same individual's control measurements. Comparison across the dose groups at a given time were made to different individuals in the other groups, and thus more statistical power is available for detecting differences from baseline within a dose group than differences from placebo across dose groups. Data are reported as mean ± SD except certain figures, in which SEM is used for clarity.

Results

There was no significant difference among the treatment groups with regard to age, weight, height, race, baseline physical examination, medical history, substance consumption, laboratory test results, or ECG. By 4 h after

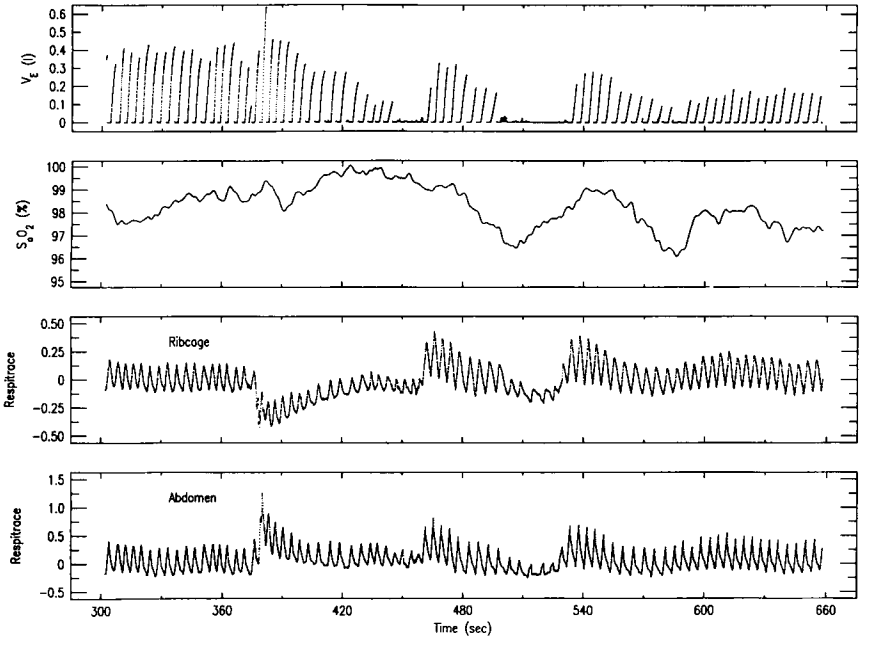

FIG. 2. Continuous (sampled digitally at 50 Hz) recording of exhaled tidal volume, pulse oximeter hemoglobin saturation, and abdominal and rib cage excursion measurements by respiratory inductance plethysmography for a single subject during (time 300–420 s) and immediately after an infusion of 2 μg/kg DMED. The Respitrace signal is a relative measure of the abdomen and thorax volumes. An increasing value indicates inhale and decreasing values indicate exhale. Note the period of apnea between time 510 and 530 s. During this period obstruction is demonstrated by the abdominal and thoracic Respitrace signals being 180° out of phase. During this recording the subject was breathing room air.

infusion all subjects were fully awake and alert, ambulatory, and able to be discharged home.

Sedation, as measured by a visual analog scale, showed a significant dose-related increase which peaked 10 min following DMED administration and declined over the remainder of the observation period. In the 1.0 (67%) and 2.0 (70%) μg/kg dose groups most subjects fell asleep (unarousable by normal volume voice command). Sedation remained significantly increased for up to 195 min after DMED in the 2.0 μg/kg group (fig. 1). Anxiety scores were low during baseline measurements in all groups and did not change (increase or decrease) in either the placebo or DMED groups.

Immediately after the infusion there was a tendency for irregular breathing with short episodes of apnea in some subjects. This effect was dose-related, occurring significantly more often in the two highest dose groups (seven of ten for 2.0 μg/kg, and five of six for 1.0 μg/kg) than in the placebo and lowest dose groups (one of six for both 0.5 and 0.25 μg/kg, and none of nine for placebo). Figure 2 shows the ventilation, Sp_{O_2} and Respitrace recordings of a subject who had pronounced apnea immediately following administration of 2.0 μg/kg of DMED. Respiratory inductance plethysmographic tracings of abdominal and thoracic movements indicate these periods were obstructive in nature and no episodes of central apnea were seen. Although there were decreases in the Sp_{O_2} corresponding to the apneic periods, the mean room-air hemoglobin oxygen saturation remained above 95% following each of the DMED doses. Sp_{O_2} decreased in the two highest dose groups beginning within 1–2 min of the termination of the infusion. The decrease in the Sp_{O_2} was greatest at 10 min in the 1.0 μg/kg group and 60 min in the 2.0 μg/kg group with decreases from 98.5 ± 0.7% to 96.2 ± 1.3% and 98.3 ± 0.8% to 95.4 ± 1.2% ($P < .05$), respectively. Following its nadir, the Sp_{O_2} gradually returned to baseline (table 1). Four subjects had Sp_{O_2} less than 94%, and the lowest Sp_{O_2} in any subject immediately following the drug infusion was 91%.

Resting ventilation was mildly decreased following 1.0 and 2.0 μg/kg of DMED. With the measured nadir occurring 60 min after infusion, the maximum change was in the 2 μg/kg group, which showed a decrease from 8.7 ± 0.7 l/min to 6.3 ± 1.5 l/min ($P < .05$; fig. 3 and table 1). This decrease predominantly reflected a reduction in tidal volume (table 1) and respiratory rate was not significantly changed except for a slight decrease (from 17.0 ± 3.5 min^{-1} to 14.2 ± 2.1 min^{-1}; $P < .05$) in the 2.0 μg/kg dose group.

Pa_{CO_2} increased after DMED infusion with the maximum effect occurring 10 min after drug administration. Statistically significant increments were noted in the 1.0 (5.0 mmHg) and the 2.0 (4.2 mmHg) μg/kg dose groups and the Pa_{CO_2} remained significantly increased through

TABLE 1. Summary of the Results for the 2.0 μg/kg Dose Group

Parameter	Time after Dose (min)								
	Baseline	10	60	105	150	195	240	285	330
VAS (mm) sedation	16.6 ± 12.4	93.2 ± 9.1*	72.4 ± 15.9*	74.6 ± 13.6*	63.3 ± 23.0*	55.2 ± 28.5*	31.3 ± 22.9	17.8 ± 11.6	10.9 ± 12.6
Spo_2 (%)	98.3 ± 0.8	96.2 ± 1.5*	95.4 ± 1.2*	96.7 ± 1.3*	97.0 ± 1.2*	97.6 ± 1.6	98.2 ± 1.3	98.1 ± 1.5	98.7 ± 1.0
$Paco_2$ (mmHg)	41.9 ± 2.3	46.1 ± 5.0*	45.3 ± 3.5*	45.5 ± 2.6*	44.0 ± 3.1	43.8 ± 2.9	43.7 ± 1.3	42.2 ± 2.2	41.6 ± 2.1
Pao_2 (mmHg)	109.5 ± 10.3	101.9 ± 14.4	117.2 ± 17.0	114.0 ± 7.6	114.6 ± 10.5	114.3 ± 12.9	112.7 ± 9.5	111.5 ± 7.7	110.5 ± 12.2
Ventilation (l/min)	8.73 ± 0.71	7.14 ± 3.04	6.28 ± 1.53*	6.87 ± 1.49	7.03 ± 0.83	7.35 ± 0.73	7.34 ± 0.81	8.49 ± 2.28	7.78 ± 1.21
Tidal volume (l)	0.47 ± 0.10	0.33 ± 0.13*	0.36 ± 0.07*	0.39 ± 0.07	0.41 ± 0.06	0.40 ± 0.05	0.41 ± 0.06	0.45 ± 0.13	0.41 ± 0.05
Slope of V_E *vs.* PET_{CO_2} ($l^{-1} \cdot min^{-1} \cdot mmHg$)	2.00 ± 0.99	1.36 ± 1.62	1.50 ± 0.79	1.28 ± 0.77	1.23 ± 0.77	1.37 ± 0.81	1.45 ± 1.02	1.65 ± 0.88	1.69 ± 0.55
Ventilation at $PET_{CO_2} = 55$ mmHg (l/min)	22.50 ± 7.32	13.82 ± 8.01*	12.89 ± 3.22*	13.68 ± 4.84*	13.08 ± 3.27*	14.72 ± 5.76*	16.54 ± 4.10*	17.70 ± 5.79*	19.56 ± 4.86
$\dot{V}_{O_2}$ (ml/min)	325 ± 33	377 ± 81*	268 ± 42	271 ± 32	285 ± 34	293 ± 36	289 ± 52	334 ± 83	308 ± 43
$\dot{V}_{CO_2}$ (ml/min)	274 ± 33	262 ± 52	214 ± 38*	232 ± 38	236 ± 29	243 ± 33	240 ± 35	272 ± 65	251 ± 37
RQ	0.88 ± 0.06	0.69 ± 0.12	0.73 ± 0.27	0.80 ± 0.16	0.76 ± 0.23	0.84 ± 0.04	0.81 ± 0.10	0.82 ± 0.05	0.84 ± 0.05
Glucose (mg/dl)	98.1 ± 8.0	123.7 ± 8.7*	109.4 ± 14.5*	102.5 ± 9.6	102.0 ± 7.3	104.0 ± 7.3	99.0 ± 9.6	96.9 ± 9.1	95.2 ± 8.6
Temperature (° C)	36.2 ± 0.5	35.9 ± 0.5	35.3 ± 0.5*	35.2 ± 0.6*	35.3 ± 0.6*	35.4 ± 0.5*	35.5 ± 0.5*	35.6 ± 0.5*	35.7 ± 0.5*

Values are given as mean ± SD. VAS = visual analog scale; RQ = respiratory quotient. * $P < .05$ different from baseline within the dose group by ANOVA and Newman-Keuls post hoc testing.
RQ is given as the average of the RQ for each subject.

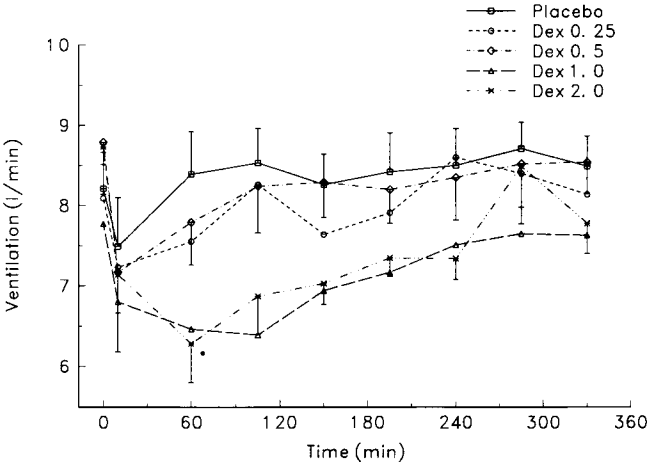

FIG. 3. Average minute ventilation while breathing room air for all dose groups. For clarity SEM is shown for the placebo and 0.5 and 1.0 μg/kg groups. Figure 1 contains explanation of the measurement times. *$P < .05$ different from the baseline (time = 0) measurements within a dose group. For the 1.0 μg/kg group a significant difference from baseline was found by ANOVA, but a specific time could not be isolated at the $P < .05$ level.

105 min in the 2.0 μg/kg group and for 60 min in the 1.0 μg/kg group. The maximum individual increase in Pa_{CO_2} was 10 mmHg (from 45 to 55 mmHg) in a subject who received 2.0 μg/kg of DMED. However, when unpaired comparisons across dose groups with respect to the placebo group were performed, no significant differences could be detected in Pa_{CO_2} at any measurement time or dose level. Arterial pH measurements were all within the clinically normal range (7.35–7.45). P_aO_2 remained unchanged throughout the experiment.

The calculated ventilation at a PET_{CO_2} = 55 mmHg showed significant changes at the two highest dose groups (fig. 4). Following DMED 1 μg/kg, resting ventilation decreased from 18.8 ± 5.3 to 11.5 ± 6.1 l/min ($P < .05$), whereas following 2 μg/kg, it decreased from 22.5 ± 7.3 to 13.8 ± 8.0 l/min ($P < .05$, table 1). Repeated hypercapnic challenges in the placebo group resulted in a 50% increase ($P < .05$) in slope by 285 and 330 min after infusion. When ANOVA was performed on all the dose groups combined, there was a significant depression in the slope compared to baseline ($P < .05$) at all time periods. However, isolation of significant differences from baseline for specific doses and times could only be done for 0.5 μg/kg at 60 min. This is most likely due to the relatively small number of subjects in each dose-time cell. However, the overall analysis does indicate a significant effect of DMED on the slope. The largest effects occurred in the 2.0 μg/kg dose group as shown in table 1. Interestingly, in the DMED groups, while there was a general increasing trend in the slopes with time, none of the slopes increased above baseline even at 330 min, as was seen in the placebo group. As with the slopes, there was a mild time-dependent stimulation of the ventilation intercepts in the placebo group, increasing from a baseline of 19.2 ± 7.9 to 27.5 ± 10.0 l/min ($P < .05$) at 330 min after infusion. The DMED groups also showed this increase with time; the three lowest doses increased above baseline by the end of the experiment, but the highest dose was still below baseline at 330 min after infusion.

The placebo group showed a stable level of oxygen consumption (337 ± 38 ml/min) and carbon dioxide production (266 ± 26 ml/min) throughout the observation period that did not differ from the baseline periods in the treatment groups. In the placebo group, there were very small, but statistically significant, increases in temperature and decreases in blood glucose by the end of the day. The temperature change was very small (from 35.7 ± 0.6° C at the start of the experiment to 35.8 ± 0.6° C at 195 min, after which it stabilized) but was very consistent among the subjects ($P < .05$). The decrease in the glucose was also very small, declining from 96.5 ± 4.6 μg/dl in the baseline periods to 91.4 ± 5.9 μg/dl ($P < .05$) by the end of the experiment.

In the 1.0 and 2.0 μg/kg DMED treated groups combined, the oxygen consumption showed a biphasic response; there was an initial increase in $\dot{V}_{O_2}$ at the 10-min measurement ($P < .05$), followed by a sharp decrease below the baseline values at the 60-min measurement ($P < .05$) and then a slow return to the baseline value by the end of the experiment. In the 2 μg/kg dose group alone (table 1), while the initial increase was statistically significant, the subsequent reduction was not. In the 1.0 μg/kg group the initial increase (23 ml/min at 10 min) and

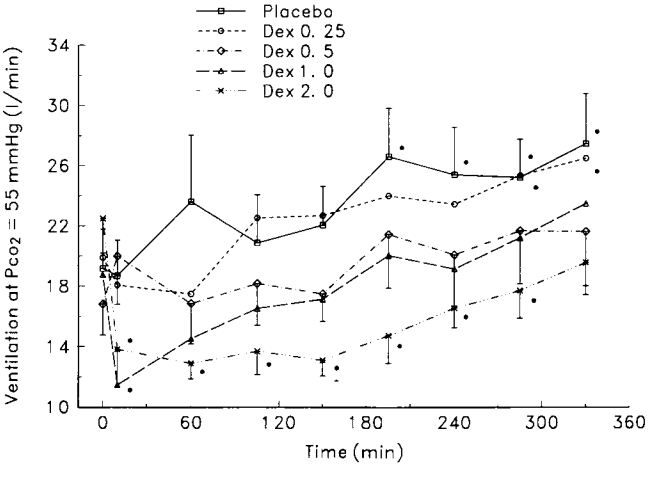

FIG. 4. Average ventilation at a PET_{CO_2} = 55 mmHg as determined by the hypercapnic ventilatory response. For clarity SEM is shown for the placebo and 0.5 and 1.0 μg/kg groups. Figure 1 contains explanation of the measurement time points. *$P < .05$ different from the baseline (time = 0) measurement within a dose group. +$P < .05$ different from the placebo measurement at the same time.

the decrease at 60 min (43 ml/min) in oxygen consumption were statistically significant ($P < .05$). This pattern was not seen in the carbon dioxide production which showed only a decline to a nadir at 60 min and then a return to baseline by the end of the experiment.

The increase in the glucose concentration following DMED was immediate and dose related (fig. 5). The glucose concentration had declined toward baseline by 60 min after infusion in all the groups, and as in the placebo group the glucose was less than baseline by the end of the experiment ($P < .05$ in the placebo, 0.25 μg/kg and 0.5 μg/kg DMED groups). Although 0.25 μg/kg group showed only a small initial increase (7 mg/dl; $P < .05$) the subsequent decline from 97.3 ± 7.3 mg/dl baseline to 85.5 ± 5.1 mg/dl at the end of the experiment was the largest.

There were small but consistent changes in the temperature in the subjects receiving dexmedetomidine. Instead of the slight steady increase in temperature seen in the placebo subjects, there was an initial decrease (0.7° C in the 2.0 μg/kg group; $P < .05$) followed by a slow increase. In the 2.0 μg/kg group, the temperature was still slightly (0.2° C), but significantly ($P < .05$) less than baseline at the end of the experiment (table 1).

Discussion

DMED caused profound sedation with most subjects in the 1.0 and 2.0 μg/kg groups falling asleep either during or shortly after the infusion. However, increasing the dose of DMED from 1.0 to 2.0 μg/kg did not significantly increase the percentage of subjects falling asleep or increase the average VAS sedation scores but did prolong these effects, indicating that sleep in most undisturbed subjects occurs following a dose of 1.0 μg/kg.

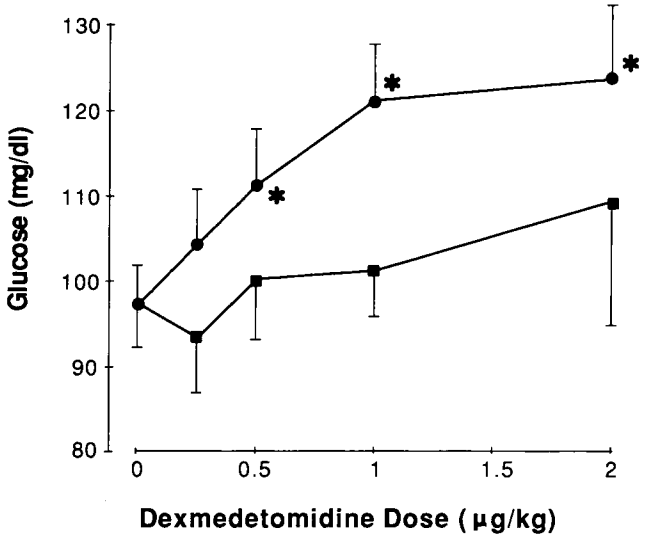

FIG. 5. Dose response for the plasma glucose measurements (mean ISD). N = 9 for placebo, N = 6 for the 0.25, 0.5, and 1.0 μg/kg groups, and N = 10 for the 2.0 μg/kg group. Values for the measurements at 10 min (filled circles) and 60 min (filled squares) post dexmedetomidine are given. *$P < .05$ different from the placebo group at the corresponding time. At 60 min a dose group difference was found by ANOVA ($P < .05$), but specific differences from placebo could not be isolated at the .05 level.

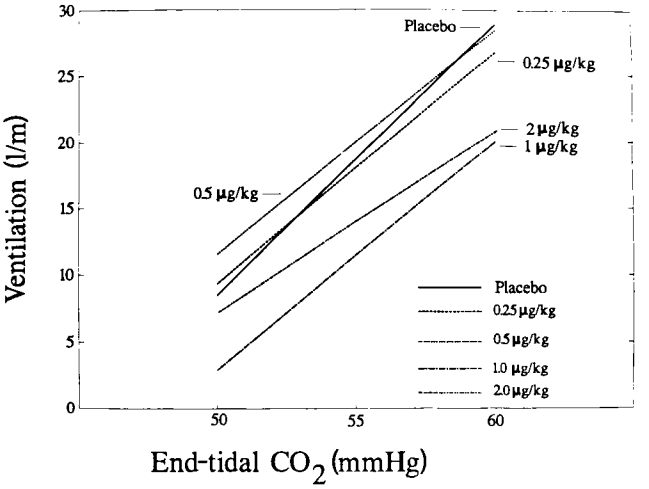

FIG. 6. Reconstructed average hypercapnic responses for all the dose groups at 60 min after the drug infusion.

DMED treatment resulted in a mild increase in resting Pa_{CO_2} and a decrease in minute ventilation with little change in the respiratory rate over the first hour following DMED. The effect of DMED on the hypercapnic response as measured by the pseudo-rebreathing test was minimal (fig. 6). The depression in the slopes of the hypercapnic response was relatively small and only significant when all dose groups were combined. There was a shift to the right of the hypercapnic response as evidenced by a change in the derived ventilation at a PET_{CO_2} of 55 mmHg (fig. 4). The pseudo-rebreathing technique has been shown to be more reliable in assessing drug effects than actual rebreathing and to give results consistent with the longer steady-state test.[23,24]

The ventilatory changes that were observed with DMED are similar to those seen following administration of other α_2 agonists,[7,8,24] including the reports by Rouge‖ and Penon,[9] who demonstrated a decrease in the ventilatory response slopes with oral and epidural clonidine respectively. However one cannot deduce from Penon's data whether the minute volume itself is decreased.

Clinically significant depression of effective alveolar ventilation is commonly caused by a reduction in central ventilatory drive, increases in deadspace ventilation, or upper airway obstruction. Such reduction in effective ventilation results in hypoxemia and hypercapnia. Hypoxemia occurs rapidly in these situations with only minimal amounts of hypoventilation if supplemental O_2 is not used. In our subjects there were no episodes of clinically

significant desaturation ($S_pO_2 < 90\%$). In this study we closely measured the ventilatory pattern while the subjects were breathing room air during and immediately after the drug infusion. Although the subjects were markedly sedated there were only transient disturbances of respiratory rhythm during the drug infusion, which resolved quickly without clinically significant arterial hypoxemia even though the subjects were breathing room air. However, our subjects were young and healthy; even the minimal ventilatory effects of DMED seen in this study could be detrimental to more frail patients with pre-existing respiratory disease.

Our observations of the subjects and review of the ventilatory data did not reveal any central apneic episodes, as have been seen with DMED in dogs,[2] and only mild episodic airway obstruction immediately after the infusion of DMED. Although more detailed study of the ability to maintain a patent airway when heavily sedated with DMED will be required, it does not appear that loss of upper airway muscle drive is a major component of the ventilatory effects of DMED.

α_2-Adrenoceptors are ubiquitously distributed throughout the CNS including in brainstem regions which are instrumental in control of breathing (*e.g.*, the nucleus tractus solitarius, nucleus ambiguous, and ventrolateral medulla[25]). As yet the function of α_2-adrenoceptors in the control of respiration has not been ascertained. Our study suggests that, in contrast to opioid mu receptors, there may be very little function of the α_2-adrenoceptors directly in neural pathways involved in the central control of breathing. Since non-REM sleep causes a decrease in the slope and a shift to the right by 3–5 mmHg of the hypercapnic ventilatory response curve,[26–28] the effects that were observed in this study may be ascribed to the sleep state induced by DMED.

Of interest is that we detected a time effect in the placebo group with the hypercapnic response slope and intercept increasing with time and becoming significantly different from baseline by the end of the day. Bailey's data also seem to indicate a similar trend but since no placebo group was used this could not be determined.[7] This effect is not due to an arterial acidemia since the arterial pH measurements were within clinically normal limits during our study. One might postulate that a cumulative CSF acidosis occurred from the performance of repeated hypercapnic response tests.

With wide involvement of adrenergic receptors both within the central and autonomic nervous systems and in many organs, it is not surprising that α_2 agonists can have wide-ranging physiologic effects besides the desired sedation, anxiolysis and analgesia. Perhaps the most striking finding of this study was the initial increase in oxygen consumption, particularly in the group receiving the largest dose of DMED. The lack of concurrent change in carbon dioxide production resulted in a decrease in the respiratory quotient ($\dot{V}_{CO_2}/\dot{V}_{O_2}$, average values from table 1 were used to calculate the ratio) to 0.70 from the baseline value of 0.84. For the same metabolic heat production, lipids require more oxygen than glucose (and produce less CO_2); thus a shift to greater oxidation of lipids may explain part of the initial increase in oxygen consumption but probably cannot be a large enough effect to be the sole cause. Since these measurements were made during a transient state (ventilation was decreasing and arterial P_{CO_2} increasing), there may have been some increase in the tissue carbon dioxide production that was not detected by respiratory gas exchange measured at the mouth because of the ability of the CO_2 stores to buffer carbon dioxide production changes. Another possible explanation for the initial increase in oxygen consumption could be an increased metabolic rate in a particular tissue (*e.g.*, myocardium). However, since oxygen consumption at rest is fairly evenly distributed among organs, it is doubtful that any one organ, during rest without skeletal muscle movements, could be the sole cause of a 16% increase in whole body oxygen consumption. This increase in oxygen consumption requires further investigation since the combination of increased oxygen consumption during a period of reduced ventilation and blood pressure[20] could be detrimental.

The subsequent concurrent reduction in both oxygen consumption and carbon dioxide production as well as the temperature decrease over the course of the DMED experiments is most likely due to the sedation, continued suppression of norepinephrine release (see accompanying paper[20]), and perhaps direct action on brainstem regulatory centers. Centrally DMED may act at the hypothalamus since administration of norepinephrine directly into the cerebrospinal fluid in primates reduces temperature and oxygen consumption through activation of alpha receptors.[29] On emergence from anesthesia shivering frequently occurs, both thermoregulatory and from the declining anesthetic levels.[30] Clonidine has been shown to reduce shivering[12,31] as well as oxygen consumption[32] upon anesthetic emergence. It also caused a small reduction in skin temperature without a change in esophageal temperature during recovery from anesthesia.[31] Although tympanic temperature should reflect central temperature, the relatively low values that we obtained may indicated that an ear canal skin temperature was being recorded. This reduction in temperature, either through cutaneous vasoconstriction or a central effect was very small and probably not of clinical significance.

Plasma glucose levels are influenced by many factors including insulin, glucagon, catecholamines, cortisol, substrate availability, and hepatic regulation. Plasma renin activity, arginine vasopressin, cortisol, and atrial natriuretic peptide have been shown to be little affected by

DMED in normal subjects, whereas human growth hormone was increased.[33] However, in aortic surgery patients vasopressin and renin were reduced by clonidine.[31] We do not have direct measurements of these factors except for catecholamines (see accompanying paper)[20] and thus cannot be conclusive about the causes of the dose-related hyperglycemia that was seen at the 10-min measurement. However, it is known that pancreatic β cells have α_2 receptors and activation of these receptors decreases insulin secretion.[34] Since the half-life of insulin is less than 9 min, a substantial reduction of insulin and consequently hyperglycemia by the 10-min measurement is consistent with our data. There do not appear to be any long-lasting alterations and no substantial undershoot to hypoglycemic levels after the peak response.

In conclusion, intravenous DMED caused marked sedation; mild hypercapnia and hypoventilation; and an early transient increase in oxygen consumption. Apart from the early transient increase in oxygen consumption, each of the other findings may be ascribed to the well-known central nervous system depressant effects of α_2-adrenergic agonists. The minimal ventilatory effects of DMED indicates that α_2-adrenergic agonists may be useful drugs in providing sedation and analgesia without ventilatory depression. However, this study was performed in healthy young subjects. In older, less healthy patients who are receiving other medications, DMED could still have clinically significant ventilatory effects.

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