Dexmedetomidine Premedication Attenuates Ketamine-induced Cardiostimulatory Effects and Postanesthetic Delirium

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Background: Dexmedetomidine is a new potent and highly selective α2-adrenoceptor agonist with sedative-hypnotic and anesthetic sparing properties. Because of its sympathoinhibitory activity, it may prove useful in balancing the cardiostimulatory effects and attenuating the adverse central nervous system effects of ketamine.

Methods: A double-blind, randomized, and comparative parallel-group study design was employed in 40 volunteers with ASA physical status 1 who were scheduled for elective superficial surgery under ketamine anesthesia. Dexmedetomidine (2.5 µg/kg, n = 20) or midazolam (0.075 mg/kg, n = 20) was administered intramuscularly 45 min before induction of anesthesia. Anesthesia was induced with 2 mg/kg ketamine intravenously, and muscle relaxation was achieved with vecuronium. After tracheal intubation, anesthesia was maintained with nitrous oxide/oxygen (2:1) and additional 1 mg/kg intravenous ketamine boluses according to clinical and cardiovascular criteria. Hypotension and bradycardia were treated by increasing the intravenous infusion rate of crystalsloids and intravenous atropine, respectively. Sedative and anxiolytic properties, intra- and postoperative drug requirements, psychomotor and cognitive impairments, and cardiovascular effects were compared between the two groups.

Results: Dexmedetomidine and midazolam proved to have equal sedative and anxiolytic effects after intramuscular administration, but dexmedetomidine induced significantly less preoperative psychomotor impairment and less anterograde amnesia than did midazolam. Compared to midazolam, dexmedetomidine decreased the need for intraoperative ketamine and was more effective in reducing ketamine-induced adverse central nervous system effects. Dexmedetomidine also was superior to midazolam in attenuating the hemodynamic responses to intubation and the cardiostimulatory effects of ketamine in general, but it increased the incidence of intra- and postoperative bradycardia.

Conclusions: These results suggest that premedication with 2.5 µg/kg dexmedetomidine is effective in attenuating the cardiostimulatory and postanesthetic delirium effects of ketamine. However, because of its propensity to cause bradycardia, routine use of an anticholinergic drug should be considered. (Key words: Anesthetics, dissociative; ketamine. Drugs: adverse effects. Hypnotics, benzodiazepines: midazolam. Intubation, tracheal; sympathoadrenal response. Receptors, adrenergic: α. Sympathomimetics: α-adrenergic receptor agonists; dexmedetomidine.)

THE development of the dissociative anesthetic ketamine represents an interesting step in our search for better intravenous anesthetics. It is a potent anesthetic with distinct analgesic activity and has a pharmacokinetic-dynamic profile characterized by a relatively rapid onset of action and immediate recovery.1,2 The precise molecular mechanism of action of ketamine has been extensively studied during the last decade, and the current understanding is that inhibition of sensory perception is mediated through N-methyl-D-aspartate receptor blockade.3 Cardiostimulatory responses after ketamine induction are possible, and recovery from anesthesia often is complicated by delirium or excitement. However, the risk for perceptual disturbances, such as unpleasant dreams or hallucinations, can be reduced by premedication with benzodiazepines.4 Although ketamine is widely used in the world, these properties have precluded its more general anesthetic use, at least in developed countries.

α2-Adrenoceptor agonists, such as clonidine and dexmedetomidine, induce sedation, reduce anesthetic requirements, and improve perioperative hemodynamic and sympathoadrenal stability,5 suggesting that they
would be suitable adjuncts to ketamine anesthesia. Compared with clonidine, dexmedetomidine, the pharmacologically active d-isomer of medetomidine, is about 10 times more selective toward the \( \alpha_2 \) adrenoceptor and acts as a full agonist in some pharmacologic test models in which the former displays only partial agonism.\(^5\)\(^6\)

The aim of the current study was to compare intramuscular dexmedetomidine and midazolam as premedication for surgery under ketamine anesthesia. Young, healthy patients undergoing a standard surgical procedure were selected for this first human study assessing this combination. Special attention was paid to the adverse cardiovascular and central nervous system (CNS) effects of ketamine.

**Methods and Materials**

*Design*

The study was double-blind, randomized, and comparative and had two parallel groups, dexmedetomidine and midazolam (20 patients in each group). The protocol was approved by the ethics committee of the Central Military Hospital and submitted to the Finnish National Board of Health. Oral informed consent was obtained from each patient.

The protocol-defined primary endpoints were preoperative sedation and anxiolysis, cardiovascular responses to intubation, intraoperative ketamine requirements, quality of postoperative recovery, and occurrence of ketamine-induced CNS symptoms.

*Subjects*

The study was performed with 40 volunteers, with ASA class 1, aged 18–24 yr, scheduled for elective superficial surgery (e.g., inguinal hernia or varico- or hydrocele). Patients with known drug hypersensitivity were excluded from the study. The sample size was based on a statistical power analysis to find a 15 beats/min difference in the heart rate (HR) response to intubation between the groups (\( \beta = 0.2 \) and \( \alpha = 0.05 \)).

The patients entered the hospital 1 or 2 days before the scheduled surgery and were interviewed and clinically examined. Routine laboratory testing was performed. All patients received zopiclone (7.5 mg, Innovine, Rhône-Poulenc Rorer, Paris, France), a nonbenzodiazepine hypnotic, orally the evening preceding surgery.

*Study Drugs and Randomization*

Dexmedetomidine (2.5 \( \mu \)g/kg, Orion Corporation Farmos, Turku, Finland) or midazolam (0.07 mg/kg, Dormicum, Roche Pharmaceuticals, Basel, Switzerland) were administered intramuscularly into the vastus lateralis muscle approximately 60 min before induction of anesthesia. These doses were considered to provide adequate and comparable preoperative sedation and anxiolysis.\(^7\)\(^9\)

Because midazolam was in a commercial dosage form, the double-blind nature of the study was maintained by having an independent nurse, not participating in the study, prepare the drug into a ready-to-inject form by diluting it into a 2-ml volume with physiologic saline. Balanced randomization was used (\( n = 20 \) for each group) with permuted blocks of ten patients.

*Study Procedure and Measurements*

Before administration of the intramuscular drugs, each patient’s baseline (mean of three recordings) HR and systolic (SBP) and diastolic blood pressure (DBP) were measured. In addition, 100 mm ungraded visual analog scales (VAS) for sedation (‘fully alert’ to ‘extremely drowsy’) and anxiety (‘fully calm’ to ‘worst possible apprehension’) were completed by each patient and psychomotor performance was quantified with the digit symbol substitution test (DSST). 10

The study drug was injected, and approximately 55 min later, before induction of anesthesia, all measurements were repeated. If the patient was asleep, sedation was recorded as 100, and the patient was awakened for other measurements. A venous cannula was inserted for intravenous infusion (6–8 ml/kg/h of Ringer’s solution perioratively). To assess anterograde amnesia, three randomly selected simple picture cards were shown immediately before induction of anesthesia, and the number of pictures recalled at the end of the post-anesthesia care unit (PACU) follow-up was recorded.

Postoperative sedation and psychomotor performance were measured 15 (VAS only) and 30 min and 1, 2, 3, 6, and 24 h after extubation. Patients’ orientation in place and time and solving of a simple mathematical problem were assessed at the same time points.

The V1 lead of the electrocardiogram (Olli Monitor 431D, Kone, Espoo, Finland, or Lifescope 6, NIHON Kohden, Tokyo, Japan) was monitored throughout the preinduction, induction, and intra- and postoperative periods. SBP and HR were monitored with automatic oscillometric devices (Colin Press-Mate, Colin Electronics, Hayashi Komaki, Japan, or Datascope Accutor
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I. A. Datascpe, Paramus, NJ), and arterial hemoglobin oxygen saturation transdermally with pulse oximeters (Oscar, Datex, Helsinki, Finland, or Biox 3700, Ohmeda, Boc Group, Louisville, KY). The end-tidal carbon dioxide concentration was monitored intraoperatively with a capnometric device (Cardiopac, Datex), and muscle relaxation was monitored with a peripheral neurostimulator (Relaxograph, Datex).

Anesthesia

While the patients breathed 100% O₂ via face mask, anesthesia was induced with 2 mg/kg ketamine (Ketalar, Parke-Davis, Barcelona, Spain) intravenously. Muscle relaxation was achieved and maintained with vecuronium (Norcuron, Organon, Oss, The Netherlands); an initial 0.1-0.15-mg/kg bolus with subsequent 0.02-0.03-mg/kg incremental boluses to maintain 95% relaxation. Additional vecuronium was administered when the first twitch in a train-of-four response was observed. Artificial ventilation (Servo 900, Siemens Elema, Solna, Sweden) was adjusted to maintain an end-tidal carbon dioxide concentration of 4.5-5.5%.

After tracheal intubation, anesthesia was maintained with nitrous oxide/oxygen (2:1) and supplemental ketamine. Tachycardia, hypertension, and clinically insufficient analgesia or anesthesia were controlled with 1-mg/dose intravenous ketamine. Tachycardia was defined as an HR faster than 100 beats/min and hypertension as SBP greater than 190 mmHg. Autonomic or somatic signs of insufficient anesthesia included lacrimation, sweating, and flushing. Supplemental ketamine, however, was not administered immediately after induction nor during and after tracheal intubation.

Hypotension primarily was treated by increasing the intravenous infusion rate (250 ml of Ringer’s solution within 5 min) and additionally with vasoactive drugs. Bradycardia, defined as an HR slower than 45 beats/min was treated with 0.005 mg/kg intravenous doses of atropine (Atropin, Orion Pharmaceutica, Espoo, Finland).

After skin closure, residual neuromuscular block was reversed with 10 µg/kg glycopyrrolate and 50 µg/kg neostigmine (Robinul-Neostigmine, Wyeth, Philadelphia, PA), and nitrous oxide was discontinued. The trachea of each patient was extubated as spontaneous respiration began, and the exact times of opening of the eyes and extubation were recorded.

Postoperative Followup

The patients were transferred to the PACU and monitored for at least 3 h or until there were no signs of any drug-induced effects (e.g., excessive tiredness, reduced BP, postoperative restlessness). For control of postoperative pain, oxycodone (Oxanet, Leiras, Turku, Finland) was administered intravenously in 2-mg incremental doses in the PACU and intramuscularly in 0.14-mg/kg doses on the ward when clinically required.

Sedation and psychomotor performance were assessed several times during the postoperative period (see above). At the end of the PACU period, the possible occurrence of hallucinations, confusion, agitation, unrealistic dreams, and/or nightmares were recorded (yes or no) and assessed on a three-grade scale (1 = mild, 2 = moderate, and 3 = severe) based on patients’ subjective estimates.

Statistical Analyses

The comparability of the treatment groups with respect to the demographic, other baseline, and operational factors were examined using two-sample t test or Fisher’s exact test. The same tests, or chi-square and Mann-Whitney tests, were used for efficacy variables (frequencies or single time-point data) to detect differences between the groups. Ninety-five-percent confidence intervals (95% CI) for the treatment differences in the primary response variables are provided. The relationship between the occurrence of CNS symptoms and ketamine requirements was tested with chi-square analysis for linear trends. The median times from turning off nitrous oxide until eye opening and extubation were estimated by using product-limit method. The differences between the study groups were tested by using the log-rank test.

For repetitive data, the differences between the study groups were analyzed by using two-way repeated measures analysis of covariance. Pre-, intra- (from 10 min until 40 min after intubation), and postoperative (from extubation until the end of PACU stay) cardiovascular data were analyzed separately to characterize the time-dependency of the observed effects in more detail. Analyses of postoperative sedation and DSST performance were applied to the measurements from 15 (sedation) or 30 min (DSST) until 3 h after extubation. The values obtained immediately before the administration of the study drug were used as the covariates. In addition, DSST ratings immediately before induction of anesthesia (changes from baseline) and cardiovas-

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cular and VAS data at later times were analyzed separately using two-sample t test.
To assess the intra- and postoperative cardiovascular stability, coefficients of variation for BP and HR were calculated by using the following formula:

\[ CV\% = \frac{SD}{\text{mean}} \times 100 \]

using values recorded at 5-min intervals during the operation or at 15-min intervals in the PACU.
The analyses were performed using BMDP statistical software (Los Angeles, CA) in an integrated network system by using an IBM (DOS)-compatible microcomputer. If nonparametric tests were used, median ± quartile deviation (QD), defined as (Q3-Q1)/2, is provided instead of mean ± SD.

Results

Patient Inclusion and Surgery
Forty patients, 20 in each group, were included in the study. All patients were evaluable for efficacy and safety. The groups were comparable with respect to the demographic and operational (table 1) factors.

Preoperative Sedation, Anxiolysis, and DSST Performance
The degree of sedation before premedication was comparable between the groups (table 1). Midazolam patients, however, were more anxious at baseline \( (P = 0.008, \text{table 1}) \). A clear increase in sedation (> 50 mm in both groups) and a moderate decrease in anxiety (16–25 mm) were observed in both groups, but there were no differences between the groups \( (P = 0.34 \text{ for sedation, fig. 1}; \ P = 0.14 \text{ for anxiolysis, data not shown}) \). The 95% CIs for differences in VAS changes between the dexmedetomidine and midazolam groups were −7 to 20.2 mm for sedation and −21.2 to 3.2 mm for anxiolysis.
The DSST was not performed for the first eight patients, and thus the analyses are based on 32 patients only (15 in the dexmedetomidine group and 17 in the midazolam group). Midazolam caused a decrease in the number of digits substituted (from 33 to 23) before induction, and the difference between the groups was statistically significant \( (P < 0.001, \text{fig. 1}) \).

Cardiovascular Effects
Baseline BP and HR were similar in both groups (table 1). Compared to midazolam, dexmedetomidine induced a slight but statistically significant decrease in HR at the time of induction \( (P = 0.007) \). Preoperative BP changes were statistically not significantly different between the two groups.
Laryngoscopy and tracheal intubation elicited 38 and 47 mmHg increases in SBP in the dexmedetomidine and midazolam groups, respectively \( (P = 0.07, \text{fig. 2}) \). Increases in DBP were comparable (data not shown), but the increase in HR was less in the dexmedetomidine

<table>
<thead>
<tr>
<th>Variable</th>
<th>DEX (n = 20)</th>
<th>MID (n = 20)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>20.1 ± 0.7 (19–22)</td>
<td>20.2 ± 1.3 (18–24)</td>
<td>0.88</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>180 ± 5.7 (171–194)</td>
<td>181 ± 5.6 (173–193)</td>
<td>0.70</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>75 ± 6.4 (66–89)</td>
<td>78 ± 6.5 (67–94)</td>
<td>0.19</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>121 ± 8.5 (110–145)</td>
<td>123 ± 10.9 (100–148)</td>
<td>0.40</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>75 ± 7.9 (60–90)</td>
<td>77 ± 8.8 (50–90)</td>
<td>0.57</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>67 ± 6.3 (56–80)</td>
<td>69 ± 10.8 (56–96)</td>
<td>0.47</td>
</tr>
<tr>
<td>Baseline VAS for sedation (mm)</td>
<td>24 ± 16.9 (5–68)</td>
<td>25 ± 17.4 (0–64)</td>
<td>0.88</td>
</tr>
<tr>
<td>Baseline VAS for anxiety (mm)</td>
<td>27 ± 16.0 (0–63)</td>
<td>45 ± 24.4 (0–85)</td>
<td>0.008</td>
</tr>
<tr>
<td>Baseline DSST performance (digits/min)</td>
<td>35 ± 8.0 (24–50)</td>
<td>34 ± 5.4 (27–47)</td>
<td>0.56</td>
</tr>
<tr>
<td>Concurrent medication (yes/no)</td>
<td>1/19</td>
<td>1/19</td>
<td>1.0</td>
</tr>
<tr>
<td>Time from study drug until induction of anesthesia (min)</td>
<td>57 ± 4.2 (49–65)</td>
<td>58 ± 4.4 (49–65)</td>
<td>0.56</td>
</tr>
<tr>
<td>Duration of anesthesia (min)</td>
<td>77 ± 14.8 (56–106)</td>
<td>80 ± 18.6 (49–123)</td>
<td>0.57</td>
</tr>
<tr>
<td>Duration of surgery (min)</td>
<td>47 ± 16.7 (23–80)</td>
<td>46 ± 18.7 (20–96)</td>
<td>0.97</td>
</tr>
</tbody>
</table>

Values are mean ± SD (ranges) or counts.
DEX = dexmedetomidine; MID = midazolam; BP = blood pressure; VAS = Visual Analog Scale; DSST = Digit Symbol Substitution Test.

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DEXMЕДЕТОМІДІНІН-ВІРУС МІДАЗОЛАМУ В КЕТАМАІНІ АНАЕСТЕЗІЯ

Fig. 1. Visual analog scale ratings for sedation (top) and digit symbol substitution test performance (bottom) at baseline (BL), before induction of anesthesia (IND), and after extubation (EXT). Data are mean ± SD.

(31 beats/min) than in the midazolam group (52 beats/min, \( P < 0.001 \), fig. 2). The 95% CIs for differences in SBP and HR increases between the dexmedetomidine and midazolam groups were −19.7 to 0.7 mmHg and −31.7 to −9.7 beats/min, respectively.

Intraoperative BP and HR values were less in the dexmedetomidine group than in the midazolam group, and the differences were statistically significant (\( P = 0.006 \) for SBP, \( P = 0.01 \) for DBP, and \( P = 0.04 \) for HR). In the dexmedetomidine group, intraoperative SBP, DBP, and HR levels remained close to the baseline values, whereas in the midazolam group, approximately 15-mmHg and 10-beats/min increases were observed (fig. 2).

In the PACU, BP and HR remained at a lower level in the dexmedetomidine group than in the midazolam group (\( P < 0.001 \) for all). Also, in the dexmedetomidine group, the hemodynamic values were actually slightly less than baseline (fig. 3). Three hours after extubation, at the end of the PACU period, SBP and DBP values were 16 and 12 mmHg, respectively, and HR 16 beats/min less in the dexmedetomidine group than in the midazolam group. Six hours after extubation, DBP and HR changes from baseline were still statistically significantly different between the two groups, but at 24 h, no differences could be observed (fig. 2).

The intra- and postoperative coefficients of variation for SBP, DBP, and HR were comparable in the two groups, varying between 7.2% and 13.8%.

Respiratory Measurements
Clinically significant respiratory depression was not seen in any of the patients. Lowest recorded individual arterial hemoglobin oxygen saturation values were 95% and 97% preoperatively and 91% and 90% postoperatively in the dexmedetomidine and midazolam groups, respectively.

Anesthetic Requirements and Other Intraoperative Interventions

Less ketamine was required in the dexmedetomidine group than in the midazolam group. Fourteen (70%) midazolam patients and only 2 (10%) dexmedetomidine patients needed additional doses of ketamine (\( P < 0.001 \), table 2). The difference in the total amount of supplemental ketamine (median 80 vs. 0 mg, respectively) was statistically significant (\( P < 0.001 \)). Eight of the 14 midazolam patients required only one additional dose of ketamine, however.

Intraoperatively, 11 (55%) dexmedetomidine patients versus only 1 (5%) midazolam patient received atropine for an HR slower than 45 beats/min (\( P = 0.001 \), table 2). Three dexmedetomidine patients needed two injections. Additionally, it was necessary to increase the fluid infusion rate for hypotension in two dexmedetomidine patients (NS, table 2). None of the patients had persistent or severe hypotension, and thus vasoactive drugs were not needed. The mean total number of interventions per patient and duration of anesthesia was 0.70/h in the dexmedetomidine group and 0.84/h in the midazolam group (NS, table 2).

Recovery and Postoperative Followup
There were no differences between the groups in the specified awakening times. The median ± QD times between discontinuation of nitrous oxide to opening of the eyes and extubation were 2 ± 0.5 and 3 ± 1 min and 4 ± 1.5 and 4 ± 1.5 min in the dexmedetomidine and midazolam groups, respectively.

Dexmedetomidine-treated patients tended to be more sedated than midazolam patients in the PACU, which was revealed by a significant drug effect in two-way
repeated measures analysis of covariance (P = 0.04). Six hours and 24 h after extubation, however, there were no differences between the groups (fig. 1). An impairment in the DSST performance was evident in both groups, with gradual recovery toward the end of the PACU follow-up (fig. 1). There were no statistically significant differences between the two groups with respect to the immediate or late recovery profiles.

Postoperatively, the patients were well oriented for time and place and managed to solve a simple mathematical problem. Thirty minutes after extubation, at the ‘worst’ time point, four (20%) dexmedetomidine patients and five (25%) midazolam patients were unable to manage the task, and only one dexmedetomidine patient was not oriented at the same single time point (NS).

Ketamine-induced subjective CNS symptoms were evident more frequently in the midazolam group than in the dexmedetomidine group. Eleven (55%) midazolam patients but only one (5%) dexmedetomidine patient reported experiencing CNS symptoms when interviewed at the end of the PACU follow-up (P < 0.001,

Table 2. Summary of Intraoperative and Postoperative Drug Requirements, Ketamine-induced CNS Symptoms, and Anterograde Amnesia

<table>
<thead>
<tr>
<th>Variable</th>
<th>Study Drug</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DEX (n = 20)</td>
<td>MID (n = 20)</td>
<td>P Value</td>
</tr>
<tr>
<td>Intraoperative atropine (yes/no)</td>
<td>11/9</td>
<td>1/19</td>
<td>0.001</td>
</tr>
<tr>
<td>Intraoperative ketamine (yes/no)</td>
<td>2/18</td>
<td>14/6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Intraoperative fluids (yes/no)</td>
<td>2/18</td>
<td>0/20</td>
<td>0.49</td>
</tr>
<tr>
<td>Intraoperative interventions (1/h)</td>
<td>0.7 ± 0.7</td>
<td>0.8 ± 0.6</td>
<td>0.48</td>
</tr>
<tr>
<td>Postoperative atropine (yes/no)</td>
<td>10/10</td>
<td>0/20</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Oxydodone in the PACU (mg)</td>
<td>7.4 ± 1.7</td>
<td>7.1 ± 2.6</td>
<td>0.67</td>
</tr>
<tr>
<td>Oxydodone at the ward (mg)</td>
<td>38 ± 10.0</td>
<td>29 ± 12.3</td>
<td>0.014</td>
</tr>
<tr>
<td>Ketamine-induced CNS symptoms (yes/no)</td>
<td>1/19</td>
<td>11/9</td>
<td>0.001</td>
</tr>
<tr>
<td>Picture cards recalled (none/1/2/3)</td>
<td>0/1/6/13</td>
<td>7/4/5/4</td>
<td>0.003</td>
</tr>
</tbody>
</table>

Values are mean ± SD or counts.

DEX = dexmedetomidine; MID = midazolam; PACU = post anesthesia care unit; CNS = central nervous system.
DEXMEDETOMIDINE VERSUS MIDAZOLAM IN KETAMINE ANESTHESIA

table 2). The most common symptom was unpleasant dreams, reported by six patients. Hallucinations were experienced by two patients. CNS symptoms usually were mild (one dexmedetomidine, seven midazolam) or moderate (three midazolam), but one midazolam patient described his nightmares as severe. The incidence of CNS symptoms in the midazolam group was not related to ketamine requirements (P = 0.56), and 7 of the 11 midazolam patients with CNS symptoms received none or only one additional dose of ketamine.

Anterograde amnesia was less frequent in dexmedetomidine- than in midazolam-premedicated patients. Thirteen (65%) of the dexmedetomidine patients recalled all pictures, compared to only 4 (20%) midazolam patients (P = 0.003, table 2). None of the dexmedetomidine patients but seven (35%) midazolam patients failed to recall any of the shown picture cards.

In the PACU, ten (50%) patients in the dexmedetomidine group were given atropine for HR slower than 45 beats/min. None of the patients in the midazolam group required atropine (P < 0.001, table 2). One dexmedetomidine patient needed three injections, and three patients needed two. Five dexmedetomidine patients required atropine both intra- and postoperatively.

All patients received oxycodone for postoperative pain control. In the PACU, the total amounts of analgesic were similar in both groups (7.4 in the dexmedetomidine group vs. 7.1 mg in the midazolam group). On the ward, however, the dexmedetomidine patients needed more analgesics than did the midazolam patients (38 vs. 29 mg, P = 0.01, table 2).

Discussion

Ketamine is a phencyclidine derivative that produces a so-called dissociative anesthetic state. Its mechanism of action and pharmacodynamic profile differ from our other anesthetics. Ketamine has cardiostimulatory effects and induces perceptual disturbances, i.e., alterations in state of mood, dissociative experiences, vivid or unpleasant dreams or illusions, and even delirium, which often are seen during and after emergence from anesthesia. These problems have limited its anesthetic use mainly to high-risk patients and to special circumstances.

The cardiostimulatory effects of ketamine are at least partly due to sympathetic activation. Ketamine inhibits neuronal and extraneuronal norepinephrine uptake13 but probably produces its sympathomimetic actions mainly by direct CNS stimulation.14 α2-Adrenoceptor agonists, which induce central sympatholysis by activating presynaptic autoreceptors and which are powerful sedative-hypnotics, might be rational ketamine adjuncts. In veterinary anesthesia, the use of α2 agonists with ketamine has gained much attention and has changed clinical anesthetic practice.15-17 Experience in human anesthesiology is limited, however. In a recent study by Munro et al.,18 300 μg clonidine per os was more effective than 1.5 mg/kg intravenous lidocaine in preventing the cardiostimulatory effects of ketamine.

Benzodiazepines have been shown to be highly effective in preventing the untoward cardiovascular responses and unpleasant emergence reactions associated with ketamine anesthesia.1 Midazolam appears to be an especially good choice for such a combination: It is short-acting and water-soluble and has sedative and anxiolytic effects, making it an almost ideal preanesthetic agent. Also, the amnestic effects of benzodiazepines may be favorable in this context. Several studies have demonstrated the clinical utility of combining midazolam to ketamine in mitigating ketamine-induced adverse effects and providing total intravenous anesthesia.19,20

Nevertheless, at doses that induced comparable and clinically adequate sedation in our healthy patients, dexmedetomidine was more effective than midazolam in complementing ketamine anesthesia. Dexmedetomidine blunted the cardiovascular stimulatory effects of ketamine and attenuated but did not totally obviate the cardiovascular responses to tracheal intubation. The pharmacodynamic profile of α2-adrenoceptor agonists thus appears to be suitable for combination with ketamine. It has to be recognized, however, that our patient population and the surgical procedure did not represent the normal clinical circumstances for the use of ketamine. More relevant patient populations should be studied before any final conclusions or recommendations are made concerning this combination. The experience of dexmedetomidine in elderly patients is limited, but preliminary results have not indicated special concerns.21 One also could speculate that the possible antiischemic properties of α2 agonists22 could be beneficial in this context.

The hemodynamic results of our study are explained easily and agree with recent results with clonidine18 and preclinical experience with medetomidine or dexmedetomidine.23,24 The effects of dexmedetomidine on sympathetic tone are opposite those of ketamine, resulting in reduction of HR and BP increases. We did
not measure plasma catecholamine levels as a measure of sympathetic activity in our study, but Vainio et al. demonstrated decreased plasma norepinephrine and epinephrine concentrations after medetomidine/ketamine combination in experimental animals.

Our finding that dexmedetomidine almost totally prevented ketamine-induced adverse CNS effects is more difficult to explain. Most probably, this was not due to decreased ketamine requirements in the dexmedetomidine group, because most of the midazolam patients with CNS sequela received none or only 1 mg/kg ketamine additionally during the surgical procedure. Neither can the greater atropine supplementation in the dexmedetomidine group explain the results, because atropine premedication before ketamine administration has been shown to increase the frequency of unpleasant dreams.26 Thus, our finding that dexmedetomidine induced less amnesia but reduced the experience of adverse CNS effects compared with midazolam is unexpected. The amnestic effects of midazolam and benzodiazepines in general are well recognized.27 It should be recognized that, although the number of patients experiencing any CNS symptom differed in the two study groups (i.e., 1 vs. 11), the degree or severity of psychic sensations in general was relatively modest among our patients. Agitation or confusion was not observed by the staff in the PACU, and additional studies in more vulnerable patients or predisposing circumstances are needed to confirm our preliminary observation.

Dexmedetomidine, 2.5 μg/kg, and midazolam, 0.07 mg/kg, intramuscularly proved to be equally sedative in our healthy patients. Interestingly, dexmedetomidine-treated patients showed good performance in the DSST immediately before induction of anesthesia. In other words, they were sedated but, after being awakened, managed the psychomotor test almost unimpaired. Thus, the sedative effects of dexmedetomidine and midazolam appear to be qualitatively different. However, intramuscular dexmedetomidine has been shown to produce dose-dependent impairment of skilled performance assessed by using a series of validated psychomotor tests in healthy volunteers.28

Depending on the anesthetic technique, relatively high incidences of intraoperative4 or postoperative9 bradycardia have been reported after intramuscular dexmedetomidine. Because of the "physiologic" mechanism of action (decreased release of endogenous transmitter instead of receptor blockade), the responsiveness to anticholinergics, vasopressors, and cardiac stimulants is maintained. In the current study, dexmedetomidine increased intra- and postoperative bradycardia (defined as HR below 45 beats/min) and the subsequent use of atropine, suggesting that an anticholinergic drug should be given routinely before induction with ketamine if dexmedetomidine is added to the anesthetic regimen. Ketamine increases salivary and tracheobronchial mucus secretion, further necessitating prophylactic administration of an antialgesic.1 Glycopyrrolate, which does not penetrate the blood-brain barrier, would be a rational choice.

The current results suggest that premedication with dexmedetomidine is effective in attenuating the cardioinhibitory and adverse CNS effects of ketamine. Because of its propensity to cause bradycardia, however, routine use of an anticholinergic drug should be considered.

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References

DEXMEDETOMIDINE VERSUS MIDAZOLAM IN KETAMINE ANESTHESIA