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Dexmedetomidine, an α_2-Adrenoceptor Agonist, Reduces Anesthetic Requirements for Patients Undergoing Minor Gynecologic Surgery

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The effects of dexmedetomidine, an α_2-adrenoceptor agonist, on vigilance, thiopental anesthetic requirements, and the hemodynamic, catecholamine, and hormonal responses to surgery were investigated in healthy (ASA physical status 1) women scheduled for dilatation and curettage (D & C) of the uterus. Fifteen minutes before induction they received single iv doses of either dexmedetomidine (0.5 μg/kg; n = 19) or saline (n = 20) in a double-blind fashion. Anesthesia was induced with thiopental and maintained with N_2O/O_2 (70/30%) and thiopental. Dexmedetomidine was well tolerated and no serious drug-related subjective side-effects or adverse events were observed. The most prominent subjective effects were fatigue and decreased salivation. The total amount of thiopental needed to perform D & C of the uterus was reduced approximately 30% (from 456 ± 141 mg [mean ± SD] after saline to 316 ± 79 mg after dexmedetomidine). This was mostly due to a smaller induction dose in the group receiving dexmedetomidine. Dexmedetomidine appeared to improve the recovery from anesthesia as measured by visual analogue scales (VAS) on fatigue and nausea. The plasma concentration of norepinephrine was decreased by 56% after dexmedetomidine implying decreased sympathetic nervous activity. Systolic and diastolic blood pressure were moderately reduced after dexmedetomidine administration. The authors conclude that dexmedetomidine preanesthetic medication decreases thiopental anesthetic requirements and improves the recuperation from anesthesia with no serious hemodynamic or other adverse effects. Further studies in patients undergoing more stressful surgery are indicated. (Key words: Anesthetics, intravenous: thiopental. Premedication, α_2-adrenoceptor agonists: dexmedetomidine. Sympathetic nervous system, α_2-adrenoceptor agonists: dexmedetomidine: 4(5)-(1-(2,3-dimethylphenyl)ethyl)-imidazole.)

CLONIDINE, the prototypical α_2-adrenoceptor agonist widely employed as an antihypertensive agent, has been shown to reduce volatile anesthetic requirements.[1,2] Clonidine attenuates sympathoadrenal responses to painful (tracheal intubation or surgery[2,3]) and other stimuli (*e.g.*, sodium-nitroprusside-induced hypotension[4]). α_2-Adrenoceptor agonists activate presynaptic α_2-adrenoceptors, thus inhibiting release of norepinephrine from sympathetic nerve endings.[5] The exact mechanism of the reduction of the anesthetic requirements is unknown but it is presumed that the decrease is caused by actions on both pre- and postsynaptic α_2-adrenoceptors in the central nervous system.[6,7]

Dexmedetomidine, the pharmacologically active d-isomer of medetomidine, is a highly selective, specific, and potent α_2-adrenoceptor agonist.[6,8] Medetomidine has a considerably higher α_2/α_1-selectivity ratio than clonidine in receptor-binding experiments (1,620 *vs.* 220 in rat brain membranes[9]), and compared with the latter drug, it has more efficacy as an α_2-adrenoceptor agonist in most pharmacologic models tested so far.[9] Dexmedetomidine has been shown to effectively reduce volatile anesthetic requirements in experimental animals as measured by MAC or even to be a complete anesthetic by itself in sufficiently high doses in certain animal studies.[7,10] The aim of this study was to investigate the sedative, hemodynamic, anesthetic-reducing, and hormonal effects of dexmedetomidine as preanesthetic medication before dilatation and curettage (D & C) of the uterus in patients receiving thiopental/nitrous oxide anesthesia.

Materials and Methods

Forty healthy (ASA physical status 1) nonpregnant women scheduled for D & C were included in this study (age 44.2 ± 6.2 yr [mean ± SD], weight 63.5 ± 9.2 kg) (table 1). The patients were admitted to the hospital only for gynecologic reasons (abnormal bleeding) and none received any medication. The study protocol was approved by the Ethics Committee of Turku University Hospital and the Finnish National Board of Health. Oral informed consent was obtained from each patient.

The patients were randomly allocated to receive intravenously either 0.5 μg/kg of dexmedetomidine (n = 19; one patient was excluded due to an attack of migraine after randomization but prior to treatment) or an equal volume (1– 2 ml) of saline (n = 20). The study was conducted in a double-blind fashion.

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TABLE 1. Patient and Operation Characteristics

Drug	Patient Number	Age (yr)	Weight (kg)	Duration of surgery (min)
Dexmedetomidine	19			
Mean		43.3	61.7	6.8
SD		5.1	9.6	3.5
Saline	20			
Mean		45.1	65.3	7.6
SD		7.0	8.8	2.7
t test				
P		0.37	0.23	0.45

The patients entered the hospital 1 day before the scheduled surgery. After fasting overnight and at least 1 h of rest in the supine position the patients were transferred to the operating unit at least 30 min prior to D & C. The procedures were performed between 9 A.M. and noon in a quiet, dimly lit room with a constant light before and after D & C. Upon arrival in the operating unit, continuous monitoring of the electrocardiogram (ECG) and heart rate (HR), and noninvasive recording of systolic and diastolic blood pressure at 5-min intervals with an automated oscillometric device (Nippon Colin 203Y, Tokyo, Japan) were started. For reasons of safety the attending anesthesiologist was aware of the ECG, but not of blood pressure or the patients' side effect reports, which were recorded by a research nurse. An antecubital vein on the left arm was cannulated for administration of the preanesthetic medication and the anesthetic (thiopental, Hypnostan® 25mg/ml) as well as to collect blood samples. The cannula was kept patent with a diluted heparin solution. Blood samples (100 ml altogether) were collected 15 and 5 min prior to induction, at the end of surgery, and 30 and 60 min following recovery from anesthesia for determination of the concentrations of norepinephrine (NE), epinephrine (E), cortisol, human growth hormone (hGH), and prolactin (PRL).

Dexmedetomidine or saline was administered slowly (over 60 s) intravenously 15 min before induction of anesthesia. Anesthesia was induced with thiopental in increments of 25– 50 mg at 15-s intervals and the induction dose (dose required to suppress the eye lid reflex) was noted.[11] Anesthesia was maintained with N_2O/O_2 (70/30 %; fresh gas flow 9 l/min) using a modified Mapleson F (Jackson Reese) system. If spontaneous movement occurred, additional bolus doses of thiopental, 25 mg were given to produce a sufficient anesthesia. The time needed to regain consciousness (*i.e.*, when the patient opened her eyes at verbal command) after the termination of N_2O was recorded.

After D & C and recovery from anesthesia, the patients were observed and tested for 1 h. Impairment of vigilance was objectively assessed with the Maddox wing and the Critical flicker fusion test (CFF).[12,13] Visual analogue scales (VAS) were used to collect subjective data[14] concerning fear, anxiety, mental clouding, fatigue, dryness of mouth, nausea, headache, and pain. The patients were familiarized with the use of the Maddox wing and CFF apparatus as well as VAS on the day before the scheduled surgery. The subjects were urged to report any possibly drug-related subjective sensations, and a standardized side-effect questionnaire, including a question of intraoperative awareness, was repeated 15 and 5 min before D & C, and 10, 30, and 60 min following recovery from anesthesia.

Blood for the chemical determinations was collected into chilled polypropylene tubes with K_2 EDTA, which were stored in ice until centrifuged within 2 h at 0–4° C. The plasma samples were stored at −70° C until assayed.

Catecholamine concentrations in plasma were determined using high-performance liquid chromatography with coulometric electrochemical detection (HPLC-EC).[15] The reproducibility of the assay was tested using pooled plasma samples from previous clinical studies, and the resulting intra-assay coefficients of variation (CV) were less than 2% for NE, and approximately 10% for E in the relevant concentration ranges. All samples from one experimental session were analyzed in one assay.

The concentrations of cortisol, hGH, and PRL in plasma were analyzed using commercially available radioimmunoassay kits (SPECTRIA®, Farmos Diagnostica, Turku, Finland) with intra-assay CVs below 5% in the relevant concentration range for PRL and cortisol and below 8% for hGH.

STATISTICAL ANALYSIS

The statistical analysis was performed using analysis of variance (ANOVA) for repeated measurements with one between factor (drug) and one within factor (time). The ANOVAs were performed over two periods separated by the surgical procedure. Demographic data and thiopental doses were analyzed with Student's *t* test. A *P* value of <0.05 was considered statistically significant. The results in the text are given as means ± SD.

Results

The two groups were similar in weight and age and duration of surgery (table 1). Dexmedetomidine was well tolerated and no serious hemodynamic or other possibly drug-related adverse events were observed. None of the patients experienced awareness under anesthesia.

Ten minutes after dexmedetomidine administration, patients experienced sedation and dryness of mouth as measured by VAS ($P = 0.0031$ and $P = 0.0037$, respectively; figs. 1 *A* and *B*). There was no difference between the two groups in mental clouding as measured by VAS before D & C ($P = 0.14$; fig. 1 *A*). The objective evaluation

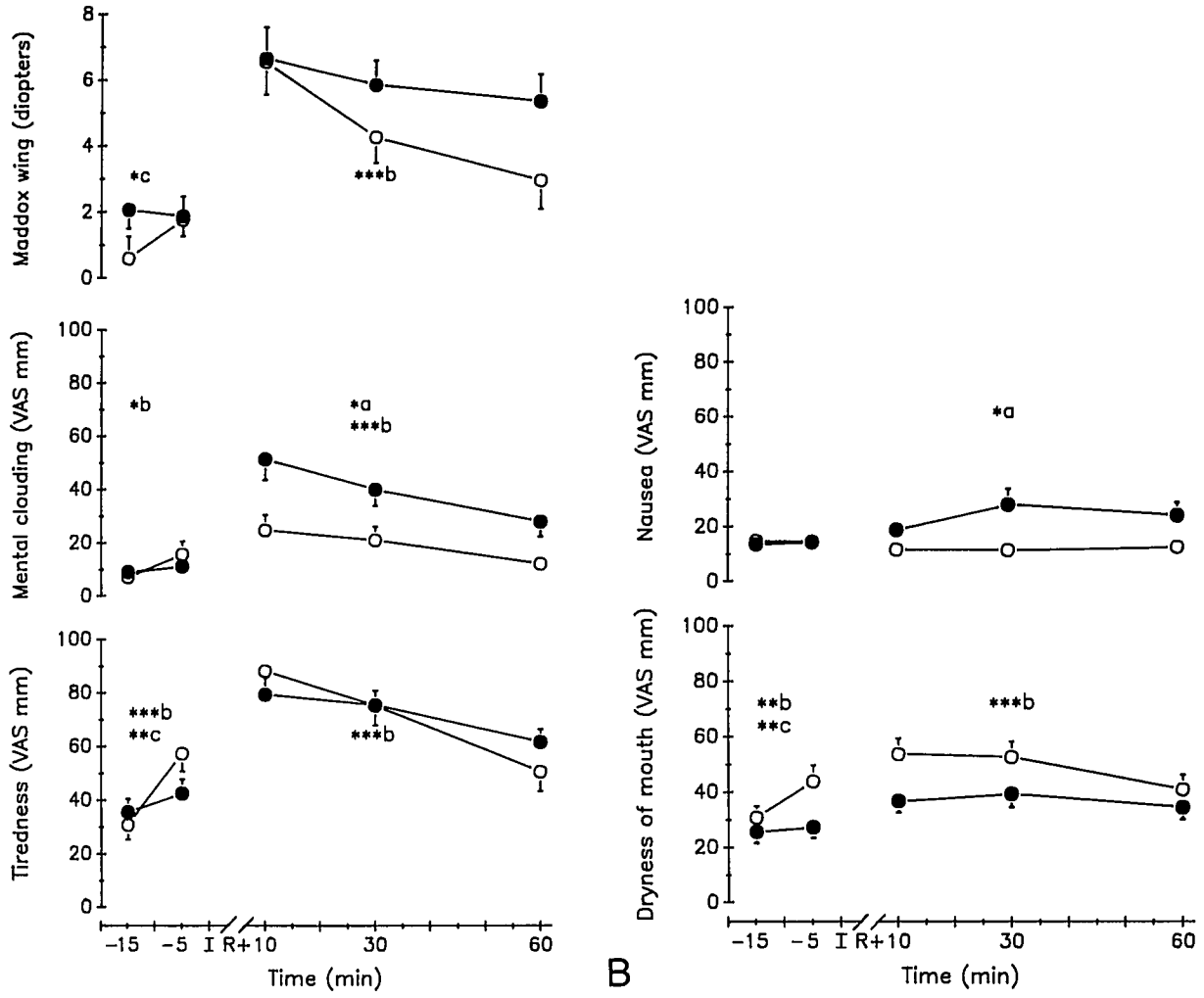

FIG. 1. *A* Mean values (±SEM) for subjectively estimated tiredness, mental clouding (as mm on a 100-mm-long visual analogue scale: 0 = fully alert or no confusion; 100 = asleep or very confused), and the Maddox wing readings (in diopters). *B* Mean values for subjectively estimated dryness of mouth and nausea (0 = normal salivation or no nausea; 100 = very dry mouth or strong nausea). Dexmedetomidine 0.5 μg/kg (○) and saline (●). I = induction of anesthesia. R = recovery from anesthesia. a = drug effect. b = time effect. c = drug × time interaction (ANOVA). $*P < 0.05$. $**P < 0.001$. $***P < 0.0001$.

of vigilance with the Maddox wing showed a statistically significant increase in exophoria (diopter readings) after dexmedetomidine administration ($P = 0.016$; fig. 1 *A*).

The induction dose of thiopental was decreased 37% by dexmedetomidine: 329 ± 100 mg after saline and 207 ± 49 mg after dexmedetomidine ($P < 0.0001$). The mean maintenance dose of thiopental was not significantly influenced by preanesthetic medication (128 ± 110 mg after saline and 109 ± 66 mg after dexmedetomidine; $P = 0.53$). The total dose of thiopental needed to maintain anesthesia for D & C was reduced approximately 31% by dexmedetomidine (456 ± 141 mg after saline and 316 ± 79 mg after dexmedetomidine; $P = 0.0005$).

There was an average decrease of 10% in systolic blood pressure after dexmedetomidine administration ($P < 0.0001$; fig. 2). There was some variation of systolic blood pressure during D & C, but it was consistently lower in the dexmedetomidine group than in the saline group until the end of the follow-up ($P = 0.038$).

Dexmedetomidine administration caused an approximately 9% decline in diastolic blood pressure and patients in the dexmedetomidine group had lower diastolic blood pressure until the end of the procedure ($P < 0.0001$; fig. 2). After recovery the difference between the groups was no longer statistically significant ($P = 0.066$).

No statistically significant differences were seen in HR between the two pretreatment groups before, during, or after the surgical procedure (fig. 2).

Plasma NE concentrations were decreased by 56% on the average ($P < 0.0001$; fig. 3 *A*) after dexmedetomidine administration. The D & C caused a small increase in the NE concentrations in both groups but the values did not

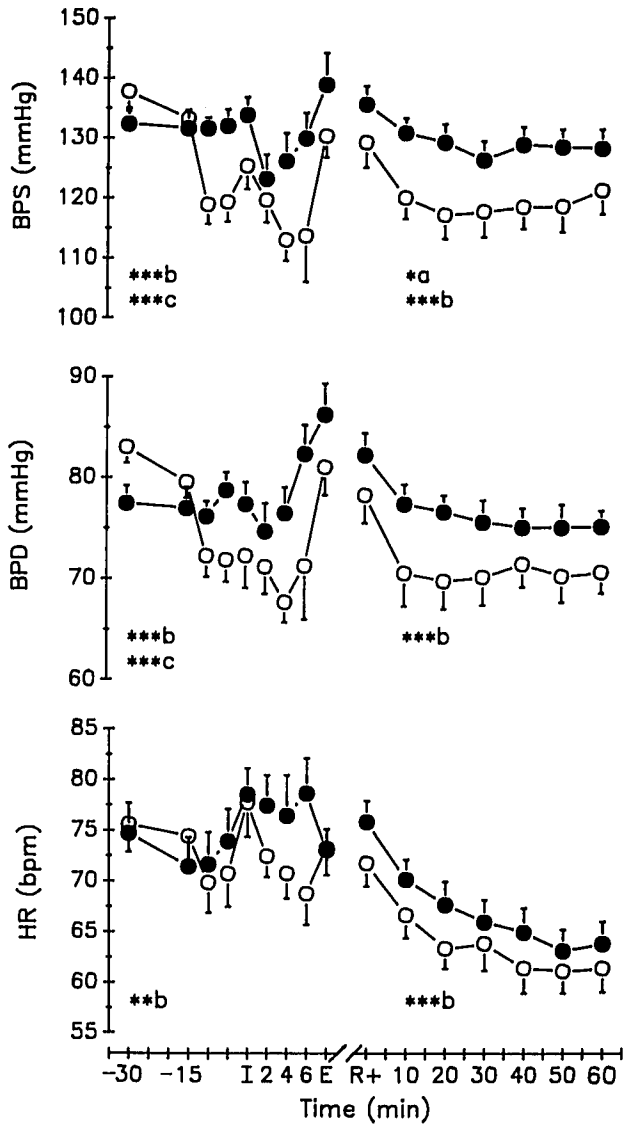

FIG. 2. Mean values (±SEM) of systolic (BPS) and diastolic (BPD) blood pressure and heart rate. Dexmedetomidine 0.5 μg/kg (○) and saline (●). I = induction of anesthesia. E = end of the operation. R = recovery from anesthesia. a = drug effect. b = time effect. c = drug × time interaction (ANOVA). *$P < 0.05$. **$P < 0.001$. ***$P < 0.0001$. Note the different time scale during anesthesia.

reach the baseline in the dexmedetomidine group. The difference between the groups lasted until the end of the experiment ($P = 0.035$; fig. 3 *A*). There were no consistent changes in the plasma E concentrations in either group (data not shown).

After D & C plasma hGH concentrations were increased more in the dexmedetomidine than in the saline group ($P = 0.0001$; fig. 3 *A*). The plasma PRL and cortisol concentrations were equally increased in both groups ($P = 0.40$ and $P = 0.85$, respectively; fig. 3 *B*).

The mean time required to regain consciousness was 8.8 ± 10.6 min in the dexmedetomidine group and 6.0 ± 5.4 min in the saline group ($P = 0.30$). The patients in the dexmedetomidine group reported less mental clouding ($P = 0.011$) but not significantly less sedation after anesthesia and D & C than those in the saline group ($P = 0.081$; fig. 1 *A*). The Maddox wing (fig. 1 *A*) and CFF (data not shown) did not reveal significant differences between the groups in postoperative vigilance.

There was significantly less nausea ($P = 0.036$; fig. 1 *B*) in the dexmedetomidine group than in the saline group after the recovery as measured by VAS. There were no significant differences in the experience of headache, pain, fear, or anxiety (data not shown). One patient in the dexmedetomidine group required analgesic supplementation (Oxycodone 5 mg iv and 5 mg im).

Discussion

Dexmedetomidine was well tolerated and no serious side effects or adverse reactions occurred in the present study. Blood pressure was modestly decreased by the dose of dexmedetomidine used but heart rates were not significantly different between the groups. These hemodynamic effects are in accordance with previous studies in healthy male volunteers.[16,17] The most prominent subjective effects were fatigue and dry mouth. The objective evaluation of the level of vigilance with the Maddox wing supported the subjective estimates on fatigue.

The most striking finding of the present study was the reduction (about 30%) in the amount of thiopental needed for D & C. A decrease in central noradrenergic neurotransmission is associated with a reduction in anesthetic requirements as reflected by a lower MAC.[18-20] We measured the NE concentration in venous blood as an index of peripheral sympathetic nervous system activity. The plasma NE concentration was markedly reduced in patients receiving dexmedetomidine. This decrement in neuronal NE release may explain in part the reduction in thiopental requirements, although recent animal studies have suggested a more direct effect of dexmedetomidine on the molecular mechanisms mediating the anesthetic response.[6,7]

A possible limitation of this study may have been the use of subjective criteria in determining the thiopental dose for each patient. Although the recording of blood pressure and subjective drug effects was carried out by a research nurse and not communicated to the anesthesiologist in charge of the patient, knowledge of the ECG (as described before) could have influenced the amount of thiopental administered. HR was indeed reduced in some patients, thereby unblinding the clinician administering the anesthetic. However, this did probably not influence the results, as the mean heart rates were not significantly different between the groups, and as there was no significant correlation between the reduction in HR after dexmedetomidine and the induction dose of thio-

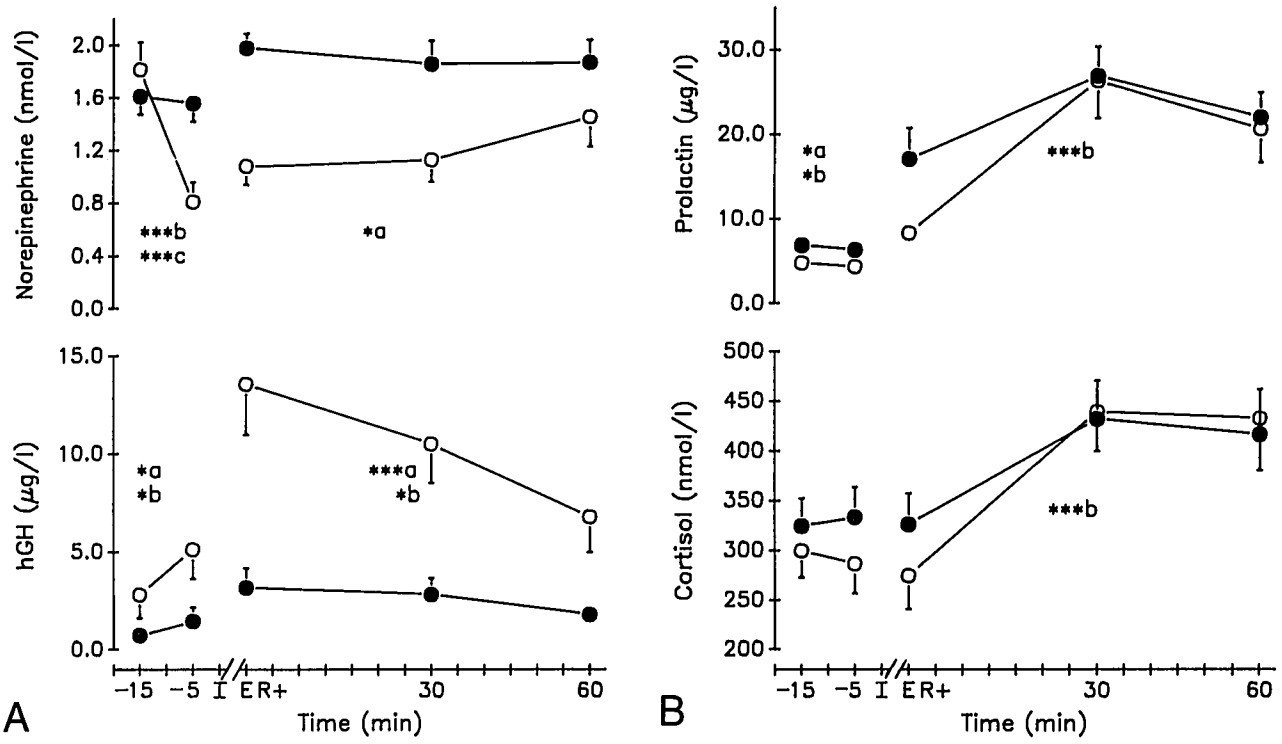

FIG. 3. *A* Mean (±SEM) plasma norepinephrine and hGH concentrations. *B* Mean (±SEM) plasma prolactin and cortisol concentrations. Dexmedetomidine 0.5 μg/kg (○) and saline (●). I = induction of anesthesia. R = recovery from anesthesia. E = end of the operation. a = drug effect. b = time effect. c = drug × time interaction (ANOVA). $*P < 0.05$. $**P < 0.001$. $***P < 0.0001$.

pental (r = −0.28). Further studies using objective criteria for determination of the anesthetic requirement and a more effective blinding arrangement are needed to confirm our results.

The maintenance dose of thiopental needed for D & C was not similarly reduced by dexmedetomidine. Although dexmedetomidine exhibits anesthetic properties, as implied by the decreased induction requirements of thiopental, it may not possess very potent analgesic activity at the dose level employed by us. Thus, when the surgery caused pain, additional thiopental was needed to maintain a sufficiently deep level of anesthesia.

Attenuation of sympathoadrenal responses, as previously reported after clonidine during more stressful surgery,[21] was not, however, clearly seen perhaps due to the relatively minor stress induced by the procedure. This may have been caused partly by the sampling of peripheral venous plasma in this study. It is well known that small changes in catecholamine release are more accurately reflected in central venous blood samples.[22] All catecholamine values were in the normal physiologic range, and the small surgery-related increases were clinically insignificant. The catecholamine measurements, as well as the other stress hormone determinations, were here used as indicators of the pharmacologic mechanism of action of dexmedetomidine and its influence on the endocrine response to anesthesia and surgery. Hormone responses have been widely used for this purpose in premedication studies,[23] and further studies with dexmedetomidine preceding more stressful procedures are required for the evaluation of the significance of the hormonal effects of dexmedetomidine in contrast to other anesthetic agents.

Clonidine and other α_2-adrenoceptor agonists stimulate hGH release.[24] In the present study, dexmedetomidine increased the plasma hGH concentration. Medetomidine, the racemic mixture of two enantiomers, has been shown to increase plasma hGH concentrations as much as 10 to 20 times the baseline values for up to 2 h in healthy male volunteers after a single iv injection.[16,25] The small increase in plasma hGH concentrations in the saline group was probably induced by the modest stress related to anesthesia and D & C, and is in accord with previous findings.[26]

α_2-Adrenoceptor agonists do not directly influence cortisol secretion under basal conditions[17,24] and clonidine does not suppress the release of cortisol in response to anesthesia and surgery.[3] Similarly, plasma cortisol levels were not affected by dexmedetomidine. Thirty minutes after recovery there was a marked increase of the plasma cortisol concentration in both groups, a well- established response to anesthesia and surgery.[23]

Stress and surgery increase the release of prolactin.[27] In the present study the concentration of PRL in plasma increased at the end of the operation in both groups. This

was uninfluenced by dexmedetomidine pretreatment, which provides further support to the lack of involvement of α_2-adrenoceptors in the regulation of PRL release, as previously reported in resting male volunteers.[25,28]

Dexmedetomidine seemed to augment the recovery from anesthesia, although the rate of the recovery was not affected as measured by Maddox wing, CFF, or the time needed to regain consciousness. Patients in the dexmedetomidine group experienced less postoperative mental clouding and less nausea than those in the saline group. This is most likely due to the decreased thiopental requirements because nausea is a common side effect of thiopental in clinical practice.[29] The present study cannot exclude the possibility that dexmedetomidine has antiemetic properties.

In summary, dexmedetomidine as preanesthetic medication decreased thiopental anesthetic requirements and improved the recuperation from anesthesia with no serious hemodynamic or other adverse effects. Further studies with dexmedetomidine as an adjuvant to anesthesia for more stressful surgery are indicated.

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