The Effect of Intravenously Administered Dexmedetomidine on Perioperative Hemodynamics and Isoflurane Requirements in Patients Undergoing Abdominal Hysterectomy

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The effects of two doses of dexmedetomidine (0.3 or 0.6 μg·kg^{-1}), fentanyl 2.0 μg·kg^{-1}, or saline as a single intravenous bolus administered 10 min prior to the induction of anesthesia were assessed in double-blind, randomized study in 96 women undergoing abdominal hysterectomy. In each patient, anesthesia was induced with thiopental 4.0 mg·kg^{-1}, and after the effect of succinylcholine had dissipated, isoflurane 0.3% end-tidal concentration in 70% nitrous oxide was begun to maintain anesthesia. The isoflurane concentration was adjusted to maintain blood pressure and heart rate within 20% of preoperative values, and fentanyl was given if the end-tidal isoflurane concentration exceeded 1.5%. In all groups, blood pressure and heart rate increased after tracheal intubation. However, the increase in blood pressure and heart rate was significantly less in the higher dexmedetomidine (0.6 μg·kg^{-1}) group than in the saline group (P < 0.01). Also, the postintubation increase in heart rate was significantly less (P < 0.05) in the dexmedetomidine 0.6 μg·kg^{-1} group (increase of 18 ± 3 beats per min) compared to the fentanyl group (increase of 26 ± 3 beats per min). In patients receiving dexmedetomidine 0.3 μg·kg^{-1}, the increase in blood pressure or heart rate did not differ from that of the saline group. The mean end-tidal isoflurane concentration was significantly less in the women receiving the higher dose of dexmedetomidine (0.35%) than in those receiving saline (0.47%) or fentanyl (0.48%), although the reduction was not clinically important. Thus, a single intravenous bolus dose of dexmedetomidine 0.6 μ·kg^{-1}, given before the induction of anesthesia, reduced the increase in heart rate in response to tracheal intubation and diminished isoflurane requirements during abdominal hysterectomy, when compared to that required by patients receiving fentanyl 2.0 mg·kg^{-1}. The clinical importance of these effects is unclear and must await studies in patients having more significant cardiovascular disease. (Key words: Anesthesia: hemodynamics. Pharmacology: dexmedetomidine. Receptors: α_2-adrenergic. Sympathetic nervous system: α-adrenergic agonist; dexmedetomidine.)

α_2-ADRENERGIC AGONISTS produce sedation[1] and have been shown to reduce anesthetic requirements.[2–4] In clinical studies α_2-adrenergic agonists have been used for their hemodynamic stabilizing effect[5–7] and anesthetic-sparing effects during cardiopulmonary bypass,[8] during cardio-

vascular surgery[9] and in aged patients.[10] There is also evidence that clonidine provides postoperative analgesia[11] and potentiates the antinociceptive action of morphine.[12]

Dexmedetomidine, the pharmacologically active d-isomer of medetomidine (4,[5]-[1-(2,3-dimethylphenyl)-ethyl]imidazole), is a highly specific and selective α_2-adrenoceptor agonist.[13,14] The α_2:α_1-binding selectivity ratio of medetomidine is 1,620:1 compared to 220:1 for that of clonidine.[14] The racemic composition of medetomidine produces anesthesia in dogs[15–17] with a duration of action of nearly 1 h.[15] In humans, dexmedetomidine has been found to have sedative properties and to be well tolerated at the doses studied thus far.[18] It causes a dose-dependent decrease in blood pressure and heart rate associated with decreased concentration of plasma norepinephrine.[18] A single intravenous bolus of dexmedetomidine given 15 min prior to the induction of anesthesia diminished the need for thiopental during cervical dilatation and uterine curettage procedures.[19] The racemic mixture of medetomidine has sedative and anxiolytic properties when used as preanesthetic medication before dental surgery.[20]

In this first human study we evaluated the effects of dexmedetomidine 0.3 and 0.6 μg·kg^{-1} on hemodynamic responses to laryngoscopy and on requirements of isoflurane for maintenance of anesthesia in patients undergoing abdominal hysterectomy. For comparison, comparable groups of patients were treated with fentanyl or saline.

Materials and Methods

The study protocol was approved by the Ethical Committee of the Helsinki University Central Hospital and the Finnish National Board of Health. Written informed consent was obtained from each patient. The study population comprised 96 women, ASA physical status 1, aged 32–55 yr, undergoing elective abdominal hysterectomy.

A double-blind randomized trial design was applied. The patients were randomly assigned into four groups, each containing 24 patients.

On the evening prior to surgery, patients were given triazolam 0.125 mg (Halcion®, Upjohn) orally. On the day of surgery, the patients received oral diazepam 0.1 mg·kg^{-1} 45–60 min before the induction of anesthesia.

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On arrival in the operating room the patient's heart rate and blood pressure were monitored by lead II of the ECG and a noninvasive blood pressure monitor, respectively. After a 5-min monitoring period, the study drug, which was diluted in saline, was administered in a 5-ml volume. Patients received dexmedetomidine hydrochloride 0.3 or 0.6 $\mu g \cdot kg^{-1}$ (Farmos Group Ltd, Turku); fentanyl 2.0 $\mu g \cdot kg^{-1}$ (Fentanyl®, Orion, Helsinki); or saline solution (as a control). The drugs studied were injected intravenously slowly over 1 min.

GENERAL ANESTHESIA

Ten minutes after the administration of the study drugs, the patients were given glycopyrrolate 0.2 mg intravenously and vecuronium bromide 0.6 mg intravenously. Anesthesia was induced with thiopental, 4 $mg \cdot kg^{-1}$, and succinylcholine was given to facilitate laryngoscopy and tracheal intubation. After the succinylcholine-induced neuromuscular blockade had dissipated or when the patient responded to the endotracheal tube, the maintenance of anesthesia was started; it consisted of 0.3% end-tidal isoflurane concentration in 70% nitrous oxide and 30% oxygen. For further relaxation, vecuronium bromide was titrated to achieve and maintain 80% relaxation as assessed with a Relaxograph® (Datex, Finland) by administering initially 4 mg vecuronium and then additional 1-mg doses during the operation as needed. Anesthesia was maintained with isoflurane using the lowest possible concentration necessary to keep blood pressure and heart rate within 20% limits of the patient's preoperative baseline value. However, because of the chronotropic effect of glycopyrrolate, heart rate values were not taken into account until 30 min after its administration. If end-tidal isoflurane concentration was insufficient to return the hemodynamic parameters to acceptable value within 2.5 min, the concentration was increased with 0.1% steps up to a maximum of 1.5% end-tidal. Fentanyl was given in increments of 50 μg to supplement isoflurane anesthesia, when the end-tidal isoflurane concentration necessary to restore blood pressure and heart rate to prescribed levels exceeded 1.5%.

Isoflurane administration was terminated at the start of the fascial layer closure, and nitrous oxide was discontinued after skin closure. At the end of anesthesia, the neuromuscular blockade was reversed with neostigmine 2 mg and glycopyrrolate 0.4 mg intravenously.

Oxycodone (Oxanest®, Leiras, Helsinki), a narcotic analgesic similar to morphine, was given intravenously for moderate or severe pain at 0.06-mg · kg^{-1} incremental doses in the recovery room.

PARAMETERS STUDIED

1. The attending research nurse assessed sedation 2, 5, and 8 min after administration of the study drug according to the following scale: 1 = awake, eyes open; 2 = asleep, easy to arouse; or 3 = asleep, difficult to arouse.

2. Blood pressure and heart rate were recorded with an automatic blood pressure monitor (Datascope Accutor®, Datascope Corp., Japan) on the left arm. The measurements were performed at 1-min intervals after the test drug administration until 10 min after intubation, at 2.5-min intervals during the first 15 min of the operation and at 5-min intervals during the rest of the operation, and at 15 min intervals in the recovery room. If the predetermined hemodynamic end-points were exceeded, blood pressure and heart rate were again recorded at 2.5-min intervals until the hemodynamic parameters were stabilized. The baseline heart rate and blood pressure values, to which intraoperative values were compared, were taken after a 5-min stabilization period.

3. End-tidal isoflurane concentration was measured using an anesthetic agent monitor (Capnomac®, Datex, Finland). The overall mean end-tidal concentration of isoflurane during surgery and mean concentrations in every 20 min, from the beginning of anesthesia, were assessed.

4. Following induction of anesthesia, but before the administration of succinylcholine, the patients' response to pinching of the upper abdomen skin with surgical forceps was evaluated according to the method of Korttila *et al.*[21] Reaction was regarded as negative if the patient did not move and positive if she did move in any way.

5. Response to the presence of the endotracheal tube was evaluated when the succinylcholine-induced neuromuscular blockade dissipated.[22] It was regarded as negative if the patient did not show any movements and positive if the patient bucked, coughed, or swallowed.

6. Time to awakening was determined as the time interval between the termination of nitrous oxide administration and eye-opening upon request.

7. The total amount of oxycodone needed for postoperative analgesia was recorded.

STATISTICAL ANALYSIS

The statistical analysis was performed using two-way analysis of covariance (ANCOVA) for repeated measurements (blood pressure and heart rate, isoflurane concentration, oxygen saturation, and respiratory rate) to determine whether differences between various treatments in general were significant (interaction of time and treatment). When a statistically significant drug × time interaction or drug effect was present, the analysis was continued by applying contrasts for each pair of different drug levels. For demographic data and single efficacy end point (maximum heart rate and blood pressure value), one-way analysis of variance (ANOVA) was used. Kruskal-Wallis ANOVA was used for nonparametric data (sedation and amount of oxycodone). The chi-squared test was used for toleration of intubation tube and reaction to abdominal

TABLE 1. Characteristics of Patients and Anesthesia

	Saline	Fentanyl 2.0 µg/kg	Dexmedetomidine	
			0.3 µg/kg	0.6 µg/kg
Number of patients	24	24	24	24
Age (yr)	43 ± 1	43 ± 1	43 ± 1	44 ± 1
Weight (kg)	66 ± 2	66 ± 2	64 ± 2	66 ± 2
Height (cm)	164 ± 1	163 ± 1	165 ± 1	163 ± 1
Duration of anesthesia (min)	108 ± 6	98 ± 5	99 ± 6	87 ± 4

Values are mean ± SE.

pinching. A P value < 0.05 was considered statistically significant. Statistical analysis was performed with BMDP software (Statistical Software, Los Angeles, CA).

Results

The patient groups were similar with respect to age, weight, height, and duration of surgery. Demographic characteristics of the patients are shown in table 1. Total perioperative fluid administration during and after the operation did not differ among the groups. The sedative effect of the higher dose of dexmedetomidine, 0.6 $\mu g \cdot kg^{-1}$, was significantly greater than that in the saline group ($P \leq 0.01$) and was not different from that in patients pretreated with fentanyl. Eleven of the 24 patients in the higher dexmedetomidine group and 9 of the 24 patients in the fentanyl group were noticeably sleepy during the preinduction period, but all were easily arousable.

ANTINOCICEPTIVE EFFECT

Reaction to abdominal pinching was significantly inhibited by fentanyl compared to saline and both dexmedetomidine groups ($P < 0.01$) (table 2). With respect to reaction to endotracheal tube placement, there was a significant difference ($P < 0.01$) between the fentanyl group and the saline group (table 2).

BLOOD PRESSURE

Before administration of the study drugs in the operating room, blood pressure values between the groups did not differ (table 3). However, already after the administration of the study drugs during the preinduction period, the systolic blood pressure values between the pa-

tient groups differed significantly (fig. 1). After the higher dose of dexmedetomidine, 0.6 $\mu g \cdot kg^{-1}$, an initial increase of about 5 mmHg, followed by a slight decrease in systolic blood pressure, occurred ($P < 0.001$ vs. placebo). At the same time, when compared to the fentanyl ($P < 0.01$) and saline ($P < 0.001$) groups, the diastolic blood pressure was also lower in the dexmedetomidine 0.6 $\mu g \cdot kg^{-1}$ group. In all groups, the maximal increase in blood pressures occurred 1–3 min after tracheal intubation. When compared to the arterial pressure before administration of the study drugs, the maximal systolic blood pressures observed after intubation in the fentanyl and in the dexmedetomidine 0.6 $\mu g \cdot kg^{-1}$ groups were significantly less than in the saline ($P < 0.01$) or in the dexmedetomidine 0.3 $\mu g \cdot kg^{-1}$ group ($P < 0.01$). The changes in the diastolic blood pressures were similar. There were no differences in the blood pressure response between the fentanyl and the higher dexmedetomidine groups.

HEART RATE

Before preanesthetic medication, heart rates between the groups did not differ (table 3). After the administration of the study drug, but just before the induction of anesthesia, a slight increase in heart rate was observed, except in the dexmedetomidine 0.6 $\mu g \cdot kg^{-1}$ group ($P < 0.001$ vs. saline, ANCOVA). At that time the higher dose of dexmedetomidine differed from saline ($P < 0.005$, ANOVA) and from fentanyl ($P < 0.005$, ANOVA). Heart rate increased in all groups after intubation, but in the higher-dose dexmedetomidine group, the increase was significantly less ($P < 0.05$) than in the other groups when compared to the baseline value. When the maximal heart rate value after intubation was compared to the value

TABLE 2. Percent of Patients Who Reacted to Abdominal Pinching and Who Tolerated the Endotracheal Tube

	Saline	Fentanyl 2.0 µg/kg	Dexmedetomidine	
			0.3 µg/kg	0.6 µg/kg
Reacted to pinching	50	17*	54	42
Tolerated endotracheal tube	12	50*	33	29

* $P < 0.01$ versus saline, chi-squared tests.

TABLE 3. Hemodynamic Parameters before, during and after Anesthesia in Patients Undergoing Abdominal Hysterectomy

	Baseline	Time after Drug (min)			Before Intubation	Maximum after 1 h	In Recovery Room
		2	5	8			
Saline							
SBP	140 ± 4	139 ± 3	133 ± 4	134 ± 4	147 ± 3	187 ± 6	127 ± 5
DBP	81 ± 3	80 ± 3	73 ± 3	74 ± 3	83 ± 3	120 ± 5	73 ± 4
HR	76 ± 2	75 ± 2	74 ± 2	75 ± 2	92 ± 3	114 ± 3	66 ± 3
Fentanyl 2.0 μg/kg							
SBP	132 ± 4	131 ± 4	123 ± 3	125 ± 3	116 ± 4	155 ± 4	119 ± 3
DBP	77 ± 2	77 ± 2	70 ± 2	70 ± 2	64 ± 2	97 ± 4	65 ± 2
HR	76 ± 3	78 ± 3	79 ± 4	79 ± 4	84 ± 4	105 ± 4	65 ± 3
Dexmedetomidine 0.3 μg/kg							
SBP	137 ± 4	136 ± 4	125 ± 4	121 ± 4	132 ± 3	177 ± 5	128 ± 4
DBP	82 ± 3	78 ± 3	71 ± 3	70 ± 3	79 ± 2	118 ± 5	69 ± 2
HR	76 ± 2	73 ± 2	72 ± 3	72 ± 3	87 ± 3	107 ± 4	65 ± 2
Dexmedetomidine 0.6 μg/kg							
SBP	140 ± 5	143 ± 6	122 ± 4	116 ± 3	120 ± 3	164 ± 5	120 ± 4
DBP	83 ± 2	80 ± 3	70 ± 2	66 ± 2	70 ± 2	106 ± 3	68 ± 2
HR	70 ± 2	61 ± 2	61 ± 2	61 ± 2	74 ± 2	91 ± 3	64 ± 2

Values are mean ± SE.
SBP = systolic blood pressure (mmHg); DBP = diastolic blood pressure (mmHg); HR = heart rate (beats per min) after drug = after study drug administration; before intubation = just before intubation.

obtained 1 min before intubation, only the dexmedetomidine 0.6 $\mu g \cdot kg^{-1}$ group differed from that of the saline group ($P < 0.05$) (fig. 2).

Postoperatively, two patients in the dexmedetomidine 0.6 $\mu g \cdot kg^{-1}$ group and one patient in each of the other groups required atropine for bradycardia (heart rate less than 40 beats per min). Bradycardia improved immedi-

ately thereafter, and none of the patients required a second dose.

ANESTHETIC REQUIREMENTS

The mean isoflurane concentration required to maintain the heart rate and blood pressure within 20% limits of the preoperative values are presented in table 4. The
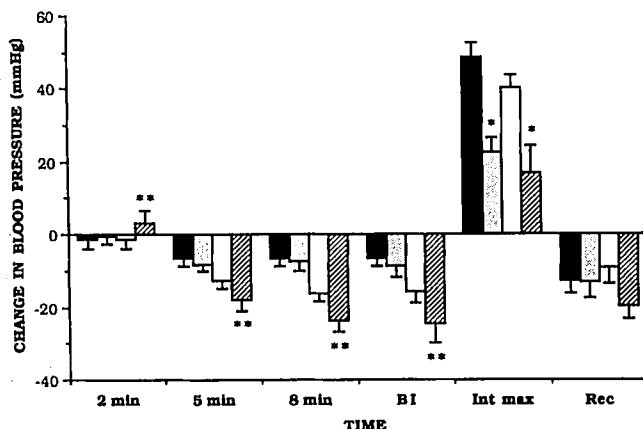

FIG. 1. Changes in systolic blood pressure (mean ± SE) 2, 5, and 8 min after administration of the study drugs, before induction of anesthesia, after endotracheal intubation, and postoperatively, compared to values obtained before administration of study drug in the operating room. BI = just before induction; Int max = highest value measured 1–3 min after intubation; Rec = 1 h after surgery, in the recovery room. Dexmedetomidine 0.6 μg/kg differed significantly from the other groups ($P < 0.001$) during the period from administration of study drugs to the induction of anesthesia. Among the other groups no significant differences appeared. After intubation, with group comparisons dexmedetomidine 0.6 μg/kg and fentanyl differed from saline ($P < 0.01$)** and fentanyl from dexmedetomidine 0.3 μg/kg ($P < 0.05$).* In the recovery room, no differences among groups appeared. Bars: filled = saline; dotted = fentanyl; open = dexmedetomidine 0.3 μg/kg; and hatched dexmedetomidine 0.6 μg/kg.
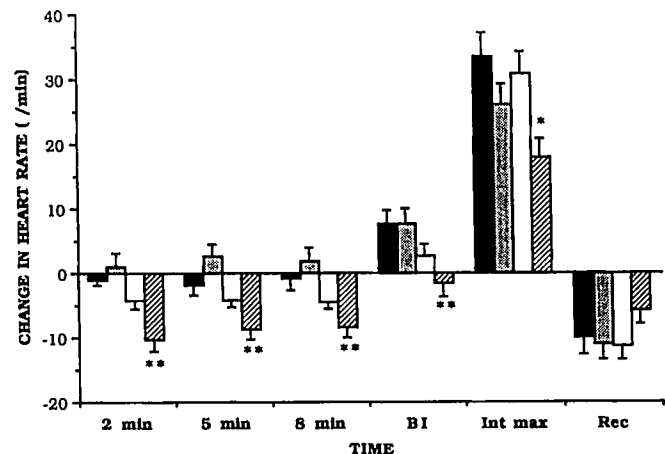

FIG. 2. Changes in heart rate (mean ± SE), 2, 5, and 8 min after administration of study drugs, before induction of anesthesia, after endotracheal intubation, and postoperatively, compared to values obtained before the study drug in the operating room. BI = just before induction of anesthesia; Int max = highest value measured 1–3 min after intubation; Rec = 1 h after surgery, in the recovery room. Dexmedetomidine 0.6 μg/kg differed significantly compared to all other groups ($P < 0.001$),** and dexmedetomidine 0.3 μg/kg differed from fentanyl during the period from administration of the study drugs to induction of anesthesia. After intubation only dexmedetomidine 0.6 μg/kg differed from all others ($P < 0.05$).* In the recovery room, no differences among groups appeared. Bars: filled = saline; dotted = fentanyl; open = dexmedetomidine 0.3 μg/kg; and hatched dexmedetomidine 0.6 μg/kg.

TABLE 4. Isoflurane Requirements (end-tidal concentration, percent) during Maintenance of Anesthesia

	Saline	Fentanyl 2.0 µg/kg	Dexmedetomidine	
			0.3 µg/kg	0.6 µg/kg
Overall isoflurane concentration (%)	0.47 ± 0.04	0.48 ± 0.05	0.38 ± 0.03	0.35 ± 0.02*
0–20 min	0.34 ± 0.01	0.35 ± 0.02	0.36 ± 0.03	0.30 ± 0†
20–40 min	0.51 ± 0.06	0.53 ± 0.07	0.40 ± 0.04	0.34 ± 0.03†
40–60 min	0.61 ± 0.09	0.62 ± 0.09	0.38 ± 0.05	0.41 ± 0.06†
60–80 min	0.49 ± 0.06	0.36 ± 0.02	0.38 ± 0.05	0.35 ± 0.05†
Patients (%) requiring fentanyl	29	25	12	4

Values are mean ± SE.
Time 0 denotes beginning of isoflurane administration. Percent of patients denotes those patients who required administration of fentanyl during the operation.

* $P \leq 0.05$, Kruskall-Wallis, one-way ANOVA among all groups.
† $P \leq 0.05$. Dexmedetomidine 0.6 µg/kg differed from fentanyl and saline, analysis of covariance for repeated measurements during the study period 0–80 min.

mean end-expiratory concentration of isoflurane required during anesthetic maintenance for hysterectomy was 25% less in the higher-dose dexmedetomidine group compared to that in the saline and fentanyl groups ($P < 0.05$). During the 20–60-min period after the start of inhalation anesthesia, when the most stressful manipulations occurred (placement of retractors and the detachment of the uterus), isoflurane requirements were more than 30% less in the patients receiving dexmedetomidine 0.6 µg · kg^{-1} than in each other groups. There was no significant difference in the number of patients requiring supplemental fentanyl (table 4).

In the recovery room, there were no differences among the groups in blood pressure, heart rate, oxyhemoglobin saturation, or respiratory rate or in the incidence of nausea and vomiting, the awakening time, or the need of postoperative analgesics. Even though the study protocol resulted in relatively light anesthesia, during interviews on the 1st postoperative day, none of the patients complained of intraoperative awareness.

Discussion

The major findings of this study were that dexmedetomidine preanesthetic medication at a dose of 0.6 µg · kg^{-1} blunted the tachycardiac and hypertensive responses to laryngoscopy and endotracheal intubation. It also diminished isoflurane requirements during surgery, although the reduction was not clinically important. Because there was no prior experience with dexmedetomidine using the current anesthetic paradigm, relatively low single doses of the compound were selected. In our study, a single dose of fentanyl was chosen for the active control treatment, which, however, might have changed the volatile anesthetic requirement, if repeated. Most patients required fentanyl to supplement inhalation anesthesia, and in these patients it was administered because of tachycardia. With the doses of dexmedetomidine used in this study, the response to abdominal pinching or to the toleration of the endotracheal tube was not appreciably attenuated.

Particular attention was paid to maintaining the double-blindness of the study. Thus, the anesthesiologist in charge of the patient remained unaware of the slight hemodynamic changes that occurred during the preinduction period. During this time the research nurse took care of the patient. Also, during surgery, the administration of all anesthetic drugs was performed strictly according to predetermined hemodynamic end points. Because of the lack of good clinical indices to determine the anesthetic depth, hemodynamic end points were employed. It may be argued that these are not optimal for assessing anesthetic depth, particularly when a hemodynamically active drug is being studied, and that the patients may actually have received unusually light anesthesia; however, this argument is not supported by the clinical observations in our study, since none of our patients complained of intraoperative awareness. Nevertheless, the possibility that the diminished isoflurane requirements may have been partly the result of bradycardic effect of dexmedetomidine cannot be totally excluded.

A consistent feature of dexmedetomidine administration is the occurrence of bradycardia.[18] Therefore, all the patients studied were given glycopyrrolate to limit the bradycardia. Excessive bradycardia seemed not to be a problem during this study. Postoperatively, three subjects treated with dexmedetomidine and two in the other groups developed bradycardia that was easily treated. However, there are clinical situations in which the sympatholytic or bradycardic actions of α-agonists may be deleterious (e.g., in the hypovolemic patient or in patients with a fixed stroke volume).

In the current study, the higher dose of dexmedetomidine, 0.6 µg · kg^{-1}, reduced the isoflurane requirements by 25%. It should be stated that this 25% reduction represents an approximately 10% reduction in overall MAC equivalents (since 70% nitrous oxide was also being given), which is not clinically important. Our data on the anesthetic-sparing action of dexmedetomidine can be added to the wealth of material demonstrating a similar action for clonidine, the prototypic $α_2$-adrenergic agonist.[2–6,8,9]

In contrast to clonidine, medetomidine and its active *dextro*-isomer, dexmedetomidine, are complete α_2-adrenagonists.[14]

The α_2-adrenergic agonists inhibit central noradrenergic transmission.[23] The ability of α-adrenergic agonists to decrease anesthetic requirements has been previously ascribed to their effect on central sympathetic transmission,[24] since decreases in noradrenergic neurotransmission have been associated with a lowering of the MAC values of volatile anesthetic agents.[25,26] However, a recent study with dexmedetomidine has suggested that other postsynaptic α_2 mechanisms may also be involved.[27]

α_2-Adrenergic agonists may provide an alternative to currently used anesthetic adjunctive agents because of their anesthetic-sparing and hemodynamic-stabilizing effects. These agents should also be studied in patients with a history of hypertension, who are prone to harmful cardiovascular responses to laryngoscopy, endotracheal intubation, and other stressful events during surgery.[28] Overall, the current results suggest that dexmedetomidine warrants further studies to evaluate its importance and possible usefulness in clinical anesthesia.

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