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Scopolamine Prevents Dreams during General Anesthesia

Adelchi Toscano, M.D., Carlo Pancaro, M.D.,† Vito Aldo Peduto, M.D.‡*

Background: **Dreaming during anesthesia is not a well-understood phenomenon. Anticholinergic drugs are used in anesthesia as premedication, but their use to decrease the incidence of dreams and psychological adverse reactions after anesthesia is not well established. The authors therefore studied the efficacy of intramuscular atropine and scopolamine for the prevention of dreams during general anesthesia with propofol and nitrous oxide.**

Methods: **Healthy women undergoing minor gynecologic surgery were randomly assigned to receive 2.5 μg/kg scopolamine or 10 μg/kg atropine intramuscularly (n = 50/group). In both groups, anesthesia was induced and maintained with propofol as a 2.5-mg/kg bolus, followed by 12 mg · kg^{-1} · h^{-1} as a continuous infusion and 70% nitrous oxide in oxygen. Two interviews regarding dreaming activity and characteristics were conducted at 20 min and 6 h after surgery.**

Results: **None of the patients in the scopolamine group and 47% of the patients in the atropine group reported the occurrence of dreams 20 min after recovery. The results were similar at 6 h: 6% of the scopolamine group and 43% of the atropine group reported dream activity. No differences in sedation or anesthetic requirements were found.**

Conclusions: **Previous studies in animals and humans suggest that dreams are affected by drugs acting on the central cholinergic system. The current results suggest that intramuscular scopolamine prevents dreams or dream recall in healthy young women undergoing short elective surgery with propofol–nitrous oxide anesthesia.**

THE significance of dreaming during anesthesia is a poorly studied and understood phenomenon. The incidence of dreaming during general anesthesia varies between 0.5% and 60%, depending on the patient population studied and timing of the postoperative interview.[1] A 20,000-patient multicenter study reported a marked variability in the incidence of dreaming ranging from 1.1% to 10.7% of the population studied.[2]

Most patients find their dreams during general anesthesia pleasant, but some report unpleasant dreams or nightmares and find their experience distressing.[3,4] Recently, the use of Bispectral Index monitoring has been shown to decrease the incidence of dreams during anesthesia in patients at high risk of awareness,[2] but no drugs to date have been investigated for preventing this side effect.

Several drugs used during the perioperative period can alter dreaming activity during anesthesia, especially propofol, which acts on the central cholinergic system.[3,5] Cholinergic neurotransmission is also a potential mediator of general anesthetic actions.[6,7]

Scopolamine and atropine are nonselective blockers of muscarinic cholinergic receptors: Scopolamine delays rapid eye movement (REM) sleep onset in humans,[8] and atropine blocks the REM sleep–like state induced by carbachol in animals.[9] In addition, at clinical doses, scopolamine exerts an effect on the central nervous system (CNS), and atropine causes central anticholinergic syndrome, postoperative delirium,[10] and memory deficit.[11] Because neural activity of muscarinic receptors increases during dreaming, and scopolamine and atropine can exert CNS effects at clinical doses, we hypothesized that scopolamine and atropine administration equally prevents, reduces, or blocks dreaming activity or recall in patients undergoing general anesthesia.

Materials and Methods

The Hospital Ethics Committee in Perugia, Italy, approved this prospective, randomized, double-blind study, and written informed consent was obtained from 100 female patients undergoing minor gynecologic surgery who had an American Society of Anesthesiologists physical status of I or II. Patients were randomly assigned to receive one of the following medications administered 30 min before the procedure: 2.5 μg/kg intramuscular scopolamine (n = 50) or 10 μg/kg intramuscular atropine (n = 50).

Exclusion criteria were sleep disorders, a history of recent or chronic alcohol intake, and use of psychotropic or illicit drugs. Patients who received narcotics or inhalation anesthetics during anesthesia or before discharge were also excluded from the study, because the former can cause sedation,[12] and the latter are known to potentiate the effects of anticholinergic drugs on the CNS, leading to an increased incidence of postoperative restlessness or somnolence.[13]

Patients were arbitrarily considered "dreamers" if they reported at least one dream per week. In all subjects, anesthesia was induced by a second anesthesiologist, blinded to the premedication drug used, with 2.5 mg/kg propofol as a bolus, followed by a continuous infusion of 12 mg · kg^{-1} · h^{-1}. After loss of consciousness, ventilation was assisted manually using a 70% nitrous oxide and oxygen mixture through a facemask until the end of surgery. If the mean arterial blood pressure or the heart rate increased above 20% of the baseline value or, if we saw any clinical signs of light anesthesia (patient movement), an additional bolus of 50 mg propofol was given;

* Staff, ‡ Professor and Chairman, Department of Anesthesiology and Intensive Care, University of Perugia. † Anesthesia Resident, Department of Anesthesiology, Pain and Perioperative Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts.

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Address correspondence to Dr. Pancaro: Department of Anesthesiology, Pain and Perioperative Medicine, Brigham and Women's Hospital, Harvard Medical School, 75 Francis Street, 02115 Boston, Massachusetts. carlopancaro@hotmail.com.

conversely, if the mean arterial blood pressure decreased below 20% of the baseline value, a 10-mg bolus of intravenous ephedrine was administered. At the end of the procedure, propofol infusion and nitrous oxide were turned off. Patients were moved to the recovery room, where a blinded investigator conducted the postoperative interview on dreaming activity 20 min after the suspension of propofol. Six hours later, at the time of the patient's discharge from the hospital, another such interview was conducted. Patients were asked whether they had had any dreams and whether the dream content was pleasant or unpleasant. In addition, it was judged by the investigator whether the characteristics of dreams were related to surgery. Patient's sedation was evaluated using the Ramsay sedation score on a six-point scale (1 = anxious and agitated patient; 2 = cooperative patient; 3 = asleep patient, brisk response to loud voice; 4 = asleep patient, sluggish response to loud voice; 5 = no response to loud voice; 6 = no response to pain); patients were classified as sedated if the Ramsay sedation score was greater than 2.[14]

Concentrations of end-tidal carbon dioxide, oxygen, and nitrous oxide were measured with an infrared gas analyzer (Capnomac Ultima, Datex, Finland) and kept in a range of 30–40 mmHg, 21–30%, and 65–70%, respectively. Heart rate, oxygen saturation, and noninvasive blood pressure were monitored before premedication and throughout the surgical procedure.

Statistical Analysis

Results are presented as mean ± SD. The Student *t* test was used to compare anthropologic data; the Fisher exact test was used to compare the difference in dreaming; and the chi-square test was used to compare the differences in sedation, additional propofol used, and ephedrine administration between the two groups. Sample size was calculated on the basis of a small pilot study looking at the incidence of postoperative dreams as the outcome variable. A minimum detected difference of 30% in dream incidence between the different premedication groups (scopolamine and atropine) was considered statistically significant. For a power of 0.8 and $\alpha = 0.05$, a sample size of 44 patients in each group was calculated to be appropriate. For an expected 10% nonadherence to the protocol (use of narcotics or inhaled anesthetics during the perioperative time), 6 additional patients per group were included. $P < 0.05$ was considered statistically significant.

Results

The two groups were homogeneous for demographics (age, 27 ± 6 yr; age range, 19–39 yr; height, 159 ± 11 cm; weight, 64 ± 12 kg), duration of anesthesia (13.9 ± 2 min), and intraoperative hemodynamic data (data not shown). Three patients were excluded from the study; two needed supplementary anesthesia with inhaled anesthetics, and one received morphine during the recovery period.

"Dreamers" and "nondreamers" were equally distributed in the two groups (59% and 64% *vs.* 40% and 35% in the atropine and scopolamine groups, respectively). No differences were found between patients who required additional propofol or ephedrine between the two groups (16% *vs.* 10% required propofol; 8% *vs.* 12% required ephedrine in the atropine and scopolamine groups, respectively).

Twenty minutes after propofol infusion was stopped, none of the 48 patients receiving scopolamine and 23 of 49 receiving atropine reported dreams ($P < 0.05$). Results were similar at 6 h (3 of 48 in the scopolamine group *vs.* 21 of 49 in the atropine group; $P < 0.05$).

Six of the 48 patients (12.5%) and 4 of the 49 patients (8%) who received scopolamine and atropine, respectively, were found to be sedated (Ramsay score greater than 2) in the recovery room at the time of the first interview (P = not significant). No sedation was found at 6 h, and all patients enrolled in the study were able to be discharged home at that time. All dreams reported were pleasant or neutral, and their content was not related to the surgery.

Discussion

This is the first double-blind randomized study showing that scopolamine prevents dreams during or dream recall after general anesthesia. This is of clinical relevance, especially for patients who may report unpleasant side effects after propofol administration. The current study showed the high effectiveness of scopolamine in preventing dreams in healthy young women. Leslie *et al.*[2] showed that 2.7% of Bispectral Index–monitored patients reported intraoperative dreaming at 2–4 h compared with 5.7% in the control group and concluded that dreaming may be related to light or inadequate anesthesia in patients at high risk of awareness; in addition, young women who reported dreams were less satisfied with anesthesia. This is in contrast to the work of Hellwagner *et al.*,[15] in which the mean age of the population was 46 yr, and the current study, in which the mean age of subjects was 27 yr, and people who reported dreaming also reported satisfaction before being discharged home. In addition, Ensink *et al.*[16] compared propofol, methohexital, and etomidate anesthesia and found a high level of satisfaction with the anesthetic procedure, although there was a high incidence of dreams in all study groups. There can certainly be a difference in patient expectations related to their anesthetic, and this can vary with age and sex. Our data are not comparable to any found in the aforementioned studies, because we had a much larger difference between groups in dreaming incidence and used the same anesthetic agents for all patients.

Besides patient dissatisfaction, there have been several reports of perioperative nightmares, and negative psycho-

logical side effects during recovery, such as hallucinations and mutism after propofol anesthesia.[17–19] In addition, some reports suggested that a good reason to prevent dreams during anesthesia was to avoid wrongful accusations and potential legal action after sexual dreams.[4,20]

Propofol activates basal forebrain cholinergic neurons,[5] which play a major role in the physiology of dream activity. Their activation could be responsible for dreams reported after propofol-based anesthesia. In addition, the cognitive changes and the mental experience of dreaming during REM sleep are characterized by an activated electroencephalographic pattern and by enhanced central cholinergic neurotransmission.[21]

In humans, REM sleep can be delayed, decreased, or abolished by scopolamine[8]; in animals, it could be induced or inhibited by cholinergic agonists[22] or antagonists,[23] respectively. Available data are conflicting on how propofol cholinergic mechanisms relate to sedation: Pain *et al.*[5] showed that propofol's sedating action is reduced by 50% in rats pretreated with 192 immunoglobulin G–saporin, which is an immunotoxin that specifically destroys cholinergic neurons, whereas in human volunteers, propofol-induced unconsciousness can be reversed with physostigmine, an acetylcholinesterase inhibitor that causes acetylcholine to accumulate at cholinergic receptor sites.[24]

A large study reported 6% dream incidence after general anesthesia with a range from 1% to 10%[1]; dreaming was associated with the following patient characteristics: lower American Society of Anesthesiologists physical status (I or II), young age, female sex, and surgical procedure on an ambulatory basis.

The higher incidence of dreams in the current study could be because all of these factors were present at the same time in every patient enrolled. In addition, propofol use may have played an important role in the higher incidence of dreaming. Propofol has been associated with dreams since its introduction in clinical practice.[3,4,25] Kasmacher *et al.*[1] studied the quality of dreaming in 230 patients during anesthesia, reporting dreams in 60% of the group whose main anesthetic was propofol, in contrast to 11% with enflurane as a main anesthetic; all dreams were pleasant. Marsch *et al.*[26] found that when patients were questioned about perioperative dreams as soon as verbal contact was established, 43% of patients receiving propofol and 10% of patients receiving thiopental–enflurane reported having had dreams while anesthetized. Bad dreams are often considered a "form fruste" of awareness: Nordstrom *et al.*[27] had a patient who reported a bad dream on the day after surgery and had explicit recall of intraoperative events at the interview 8 days later. The quality of dreams reported in this study was pleasant at the first and second interviews, so we can assume that no patients experienced awareness although we did not interview them 1 week after discharge. In this study, propofol may have mimicked cholinergic activity in both groups and induced dreams; scopolamine may have blocked the dream activity, given its strong central anticholinergic properties.

In animals, atropine blocks the REM sleep–like state induced by carbachol,[9] and in clinical studies, atropine has been associated with an increased incidence of memory deficit after anesthesia compared with glycopyrrolate.[11] Furthermore, arousal in the first 30 min after cessation of anesthesia is delayed after administration of atropine–neostigmine but not glycopyrrolate–neostigmine mixtures, which are used to antagonize the effects of nondepolarizing neuromuscular-blocking drugs.[28] These reports prove that atropine crosses the blood–brain barrier and does have an effect on the CNS at clinically administered doses. In the current study, atropine has not been effective in preventing dream activity. It may also be that atropine, unlike scopolamine, is not absorbed rapidly and does not significantly penetrate lumbar cerebrospinal fluid after intramuscular injection.[29] Perhaps patients who received scopolamine had therapeutic cerebrospinal fluid levels of drug that exerted the central anticholinergic effects, whereas patients who received atropine did not achieve such clinically significant levels in the CNS at the dose used. It would be interesting to see whether administering the drugs intravenously would replicate our results. If we assume that the two drugs reached effective CNS concentrations, scopolamine may have exerted an amnesic effect whereas atropine did not. The amnesic effect of scopolamine results principally from a blockade of postsynaptic cholinergic muscarinic M1 transmission, leading to a disruption in the functional role of the hippocampus in working memory.[30–32]

It is unlikely that scopolamine caused an increased depth of anesthesia, because requirements for postoperative sedation, propofol rescue doses, and ephedrine were similar in both study groups. In support of our clinical data, Meuret *et al.*[24] showed that the auditory steady state response and Bispectral Index are not reduced after administration of 8.6 μg/kg intravenous scopolamine in propofol-anesthetized subjects. The scopolamine dose used in the current study was 2.5 μg/kg, less than a third of that used by Meuret *et al.* In addition, a recent large prospective cohort study showed that dreaming during anesthesia is unrelated to the depth of anesthesia in the majority of cases.[33] However, even though intraoperative vital signs and postoperative sedation were the same, the two groups still might not have had the same depth of anesthesia, and the fact that we did not use any anesthesia depth monitor represents a major fault of this study.

The total dose of propofol was similar to that used in the literature.[34] We also added 70% nitrous oxide, because this amount would reduce the risk of awareness and does not impair short-term memory[35] and would thus not interfere with our collection of postoperative data during interviews.

Our study has additional limitations. First, we did not administer scopolamine to patients in whom cardiac function was compromised or who were hemodynamically unstable. Even though vital signs did not significantly change after premedication and throughout surgery, we are not able to draw any conclusions regarding scopolamine safety in other groups of patients. Second, surgical procedures were short, and a single scopolamine dose might not be as effective in a longer procedure. Third, we tested scopolamine in people younger than 39 yr, and we do not know whether it can produce significant psychomotor slowing in younger or older patients.[36] Fourth, it would have been interesting to know whether atropine induces a higher incidence of dreams compared with placebo-treated patients, but we did not include a placebo group in the current study.

The fact that scopolamine was effective in young women raises the question of whether dream incidence would have been different in young males. Females are less sensitive than males to the anesthetic effect of propofol, recovering 40% faster at the same dose.[37] Further studies are needed to test whether male patients might have a different response to the dream-suppressant effects of scopolamine.

Patients who usually experienced more than one dream a week had a similar incidence of dreams to nondreamers during anesthesia, suggesting that intraoperative dreaming activity is not influenced by the dream habits of the patient. This result is in contrast with other studies where the frequency of dreams during home sleep was found to affect the incidence of reporting dreams during both propofol and thiopentone–enflurane anesthesia.[26]

In conclusion, dreaming during propofol-based anesthesia is common and can be effectively prevented by scopolamine injection, thus avoiding side effects and patient dissatisfaction during the perioperative period. We think additional studies are needed to determine whether scopolamine could also be effective in preventing awareness in a broader patient population.

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