Anesthesiology
62:120–123, 1985

Reduced Anesthetic Requirement after Electrical Stimulation of Periaqueductal Gray Matter

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To determine whether electrical stimulation of the periaqueductal gray region decreases anesthetic requirement, the authors studied the effect of such stimulation on the MAC of halothane and 60% nitrous oxide in 33 patients. These patients, who were undergoing implantation of a radio-frequency-coupled receiver and connection of that receiver to electrodes previously implanted in the periaqueductal gray area, were assigned randomly to receive (n = 16) or not receive (n = 17) electrical stimulation 1 h before surgery. The mean value (±SEM) for the minimum alveolar concentration of halothane combined with 60% nitrous oxide was significantly less ($P < 0.001$) for patients who were stimulated preoperatively (0.15 ± 0.05%) than for those who were not (0.51 ± 0.02%). The authors conclude that stimulation of the periaqueductal gray region decreases anesthetic requirements and believe that at least three mechanisms are possible: a nonspecific narcotic-like effect, a specific effect on a pain pathway, or an effect on specific neural pathways that affect anesthetic requirements secondary to changes in regional concentrations of neurotransmitters. (Key words: Analgesia. Brain: brain stem; periaqueductal gray matter. Pain. Potency, anesthesic: MAC.)

ELECTRICAL STIMULATION of the periaqueductal gray (PAG) matter of patients having chronic intractable pain of peripheral origin produces pain relief[1] in specific areas related to the placement of the stimulating electrode. Such specific pain relief is accompanied by an increase in beta-endorphin levels in ventricular cerebrospinal fluid (CSF)[2] but by only mild to moderate alteration in the threshold for acute pain caused by skin stimulation. Pain suppression by stimulation of the PAG area in both humans and animals is highly specific: most patients report no effects of stimulation other than analgesia, *i.e.*, no drowsiness, projected sensations, loss of skin sensation, seizures or motor signs.[1–4] While it might be inferred, therefore, that PAG stimulation would not affect anesthetic requirements, the release of beta-endorphins from such stimulation may reduce anesthetic requirements.

To determine if electrical stimulation of the PAG area affects anesthetic requirement, we studied the effect of PAG stimulation on the minimum alveolar concentration (MAC) of halothane and 60% nitrous oxide, *i.e.*, on the amount of anesthetic needed to prevent movement in response to a skin incision in 50% of patients.[5]

Methods

We obtained approval from the Committee on Human Research and informed consent to study 33 patients who had had electrodes implanted stereotactically in the PAG area to control chronic pain. The effectiveness of the electrodes was confirmed during a 1- to 2-week period of trial stimulation, during which time voltage, pulse, and waveform were varied to determine the optimum combination for achieving pain relief. At the time of study, patients were undergoing surgery to connect the electrode leads to a radio-frequency-coupled receiver implanted subcutaneously in the anterior chest wall. Patients were assigned randomly to receive (n = 16) or not receive (control, n = 17) electrical stimulation 1 h before surgery. This time was chosen because some patients experience a delay of as long as 1 h between stimulation and pain relief. Other than this preoperative stimulation, no patient used a a stimulator during the 24 h before the study or received a sedative, hypnotic, or analgesic drug during the 12 h before study. Patients were told that stimulation might increase, decrease, or leave unchanged their anesthetic requirement.

Anesthesia was induced with thiopental (1 mg/kg iv), 0–4% halothane in 60% nitrous oxide, and 40% oxygen. Lidocaine spray (160 mg/70 kg) was administered to the larynx, the endotracheal tube was inserted, and ventilation was controlled to achieve an end-tidal carbon dioxide concentration of 32 to 35 mmHg, measured by mass spectroscopy. A predetermined stable end-tidal

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Received from the Departments of Anesthesia, Medicine, Pharmacology, and Neurosurgery, University of California, San Francisco, California 94143. Accepted for publication August 9, 1984. Supported in part by grants NIGMS 15571 and NIA 1P01 AG03104-01,02. Presented in part at the annual meeting of the American Society of Anesthesiologists, St. Louis, October 1980, and at the international meeting "Pharmacological Basis of Anesthesiology," Milan, Italy, October 1983.

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concentration of halothane was maintained for at least 20 min prior to incision. Thirty to 50 min after endotracheal intubation, a horizonal skin incision was made below either the left or right clavicle, and movement in response to incision was noted. The end-tidal concentration of halothane given for the 20 min before the surgical incision was chosen using the Dixon up-and-down method.[6] That is, if a patient moved in response to skin incision, the next patient received a 0.10% higher concentration of halothane. Likewise, if the preceding patient did not move, the next patient received a 0.10% lower concentration. Body temperature was monitored with the use of an esophageal probe and was kept between 35.5° C and 37° C with the aid of a heating blanket. The end-tidal concentration of nitrous oxide was monitored with the use of a mass spectrometer (Chemtron®) that was calibrated daily. The end-tidal concentration of halothane was monitored with the use of an ultraviolet gas analyzer (Cavitron®), also calibrated daily. MAC for halothane was calculated from published data and adjusted for the age of the patient.[7,8] Thus, we measured the end-tidal concentrations of halothane and nitrous oxide. From these values, we also calculated the total MAC of anesthesia each patient received, based on age adjustments and published data for halothane and an assumed 0.54 MAC contribution for 60% nitrous oxide. The average concentration and MAC of halothane, and of halothane–60% nitrous oxide, were determined for each group by quantal analysis with the use of an iterative program.[9] These concentrations and MAC values for the two groups were compared with the use of Student's t test.[10]

Results

Stimulation of the periaqueductal gray region 1 h before surgery decreased anesthetic requirements. Including the 0.54 MAC contribution from 60% nitrous oxide, the mean (±SEM) anesthetic requirement was 0.75 ± 0.10 MAC for stimulated patients and 1.26 ± 0.03 MAC ($P \leq 0.001$) for unstimulated patients (fig. 1). The end-tidal halothane concentrations required for anesthesia were significantly ($P \leq 0.001$) less for the stimulated group (0.15 ± 0.05%) than for the unstimulated group (0.51 ± 0.02%) (fig. 1).

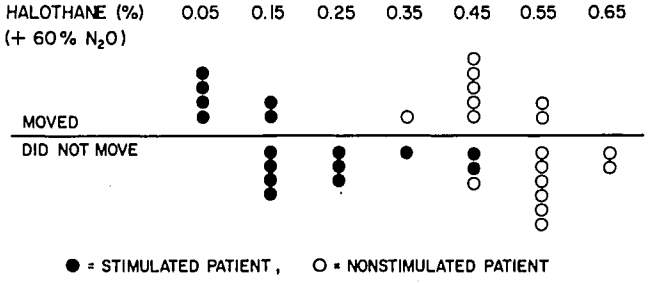

FIG. 1. Movement in response to skin incision at different concentrations of anesthesia (halothane and 60% nitrous oxide) for 16 patients who electrically stimulated the periaqueductal gray area of the brain 1 h before surgery and for 17 patients who did not. The reduction in anesthetic required to prevent movement for the patients in the stimulated group is significant ($P \leq 0.001$).

Discussion

Electrical stimulation of the PAG area immediately before surgery reduced anesthetic requirements in patients with chronic pain. Although this reduction is significant when compared with normal values reported in the literature,[7,11] chronic pain patients in the unstimulated group had a mean value for MAC that was significantly greater (by 26%) than would have been predicted from previous studies (1.0 ± 0.04).[7,8,11] We suggest that this may have resulted from an "addiction" to the chronic release of endorphins by PAG stimulation in these patients.[1–4] This hypothesis is consistent with the hypothesis (not yet proven) that chronic administration of narcotics can increase anesthetic requirements. If the small doses of thiopental (1 mg/kg) and lidocaine (160 mg/70 kg) administered for patient comfort or hemodynamic stability influenced anesthetic requirements more than 30 min later, such an event would further strengthen the suggestion that patients with chronic pain have increased anesthetic requirements.

At least three hypotheses may explain the reduction in anesthetic requirement after stimulation of the PAG area. First, reduction in MAC may be due to a nonspecific narcotic-like effect. Periaqueductal gray stimulation increases endogenous opioid-like activity in the cerebrospinal fluid (CSF).[2,4] In addition, analgesia produced by periaqueductal gray stimulation is at least partially reversible by the narcotic antagonist naloxone.[1,12–14] Several studies in animals[15,16] and humans[17–19] have shown that administration of narcotics decreases the requirement for other anesthetics. Since cross-tolerance exists between exogenous opiates and endogenous opioid peptides,[20] reduction in anesthetic requirements by release of endogenous opioid peptides after PAG stimulation would be predicted.

The second hypothesis that may explain the reduction in MAC is activation of specific pain-inhibiting pathways by PAG stimulation. PAG stimulation-induced pain relief is inhibited by destruction of specific descending pain pathways in the brain stem and spinal cord.[21] These pain pathways are modulated by serotonergic raphe neurons that are affected by PAG stimulation.[21] This mechanism seems less likely, however, since the derma-

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tome area of pain relief is highly specific and in every patient differed from the skin area in which the MAC testing incision was made.

The third hypothesis postulates that electrical stimulation induces general anesthesia by affecting specific neural transmission in particular areas of the brain. Although the structural diversity of anesthetic drugs implies that such drugs achieve their effect by causing a generalized depression of cerebral function, recent evidence implicates specific regions of brain in the creation of the anesthetic state. The PAG area is affected specifically by two general anesthetics, cyclopropane and halothane,[22] that have diverse clinical and electroencephalographic effects.[23] In the rat, both halothane and cyclopropane anesthesia cause accumulation of norepinephrine in the PAG region.[22] This accumulation is consistent with the hypothesis that anesthetic drugs produce anesthesia by selectively affecting specific regions of the brain. These anesthetics also increase serotonin in the nucleus raphe dorsalis.[24] This nucleus modulates PAG stimulation-induced pain relief.[21] Preliminary turnover experiments indicate that these accumulations of transmitters result from reduction in release of neurotransmitters from presynaptic nerve endings (unpublished observations); perhaps this reduction contributes to the production of anesthesia.[22] Consonant with this hypothesis is the fact that destruction of these regions decreases the amount of neurotransmitter available at the active site and reduces anesthetic requirement.[25]

This study implies that patients who have chronically increased opioid activity (endogenous or exogenous) might have altered anesthetic requirements. When actively deprived of the stimulus that chronically increases opioid activity, such patients may have increased anesthetic requirements. However, if such patients receive that stimulus preoperatively, they may have decreased anesthetic requirements. Individuals who might be affected in this way include long-distance runners[26] and patients who chronically receive analgesics or acupuncture.[13]

We conclude that electrical self-stimulation of the PAG area immediately before surgery decreases anesthetic requirements for surgery. This decrease may be attributable to a nonspecific narcotic effect, to a specific effect on a pain pathway, or to stimulation of a specific neurotransmitter pathway that affects anesthetic requirements.

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