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Physostigmine Prevents Postanesthetic Shivering As Does Meperidine or Clonidine

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Background: **Postanesthetic shivering develops in as many as one half of patients recovering from isoflurane anesthesia. Cholinergic stimulation of the hypothalamic-pituitary-adrenal axis and adrenal medulla by physostigmine enhances secretion of arginine vasopressin, epinephrine, and norepinephrine. Because the hypothalamus is the dominant thermoregulatory controller in mammals, and these neurotransmitters may be involved in body temperature control, physostigmine administration may influence the incidence of shivering. Accordingly, the authors tested the hypothesis that physostigmine administration inhibits postanesthetic shivering. Its efficacy was compared with that of saline (negative control) and meperidine and clonidine (positive controls).**

Methods: **Sixty patients having surgery of the ear or nose were tested. General anesthesia was induced with 2 mg/kg propofol, 0.1 mg/kg vecuronium, and 1.5 μg/kg fentanyl and maintained with isoflurane (1.5 ± 0.4%) in 70% nitrous oxide. At the end of surgery, the patients were randomly assigned to receive an intravenous bolus of 0.04 mg/kg physostigmine, isotonic saline, 0.5 mg/kg meperidine, or 1.5 μg/kg clonidine. Heart rate, mean arterial blood pressure, oxygen saturation, visual analog pain score, temperature, and postanesthetic shivering were measured during recovery.**

Results: **Postanesthetic shivering occurred in 6 of 15 (40%) patients given saline. In contrast, postanesthetic shivering was significantly reduced in physostigmine-treated patients (1 of 15, or 7%) and was absent in patients given clonidine or meperidine.**

Conclusions: **Physostigmine inhibited shivering as well as did two established treatments, meperidine and clonidine. These data suggest that cholinergic systems contribute to the genesis and control of postanesthetic shivering. (Key words: Inhaled anesthetic; nitrous oxide; pain; temperature; thermoregulation; isoflurane.)**

POSTANESTHETIC shivering seems less common than previously reported, possibly because more patients are actively warmed[1] and opioids are used in larger doses.[2] Shivering nonetheless remains a disturbing consequence of surgery and anesthesia. Most postoperative shivering appears to be thermoregulatory,[3] although volatile anesthetics *per se* may facilitate muscular activity.[4] The pathways and neurotransmitters by which signals are conveyed from hypothalamic thermoregulatory centers to skeletal muscle remain poorly understood. However, the system apparently involves multiple levels of negative feedback and many neurotransmitters.

Various pharmacologic treatments for postanesthetic shivering have been advocated. As a class, μ-receptor opioids reduce the shivering threshold.[2] Meperidine (pethidine), however, possesses special antishivering properties, possibly mediated by its kappa-receptor activity.[5] Meperidine reduces the shivering threshold

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twice as much as the vasoconstriction threshold, and twice as much as equianalgesic doses of alfentanil.[2] Many studies have also shown that clonidine effectively prevents[6] and treats[7] postanesthetic shivering. The efficacy of clonidine appears to result from central thermoregulatory inhibition because it comparably reduces the vasoconstriction and shivering thresholds.

Other, apparently unrelated, drugs are also effective treatments for postanesthetic shivering. These include the centrally acting adrenergic phenylpropylamine methylphenidate,[8] the 5-hydroxytryptamine antagonist ketanserin,[7] magnesium sulfate,[9] doxapram,[10] and hypercarbia.[11] Furthermore, shivering in animals is prevented by hypothalamic injection of norepinephrine,[12] acetylcholine,[13] and the alpha-receptor antagonist phentolamine.[14] Similarly, shivering is inhibited by intra-cerebroventricular injections of serotonin,[15] acetylcholine,[13] 5-hydroxytryptamine,[16] dopamine, and apomorphine.[17]

Physostigmine is used widely to treat the central anticholinergic syndrome. Because this drug is a cholinesterase inhibitor and readily crosses the blood-brain barrier, it is also used to treat intoxicated patients, to diagnose coma of unknown origin, and to restore vigilance after prolonged sedation.[18] Physostigmine possesses several pharmacologic actions in addition to being a central cholinergic agonist. It abolishes the somnolent effect of opioids and restores respiratory rates to predrug values.[19] In addition, 2 mg physostigmine produces analgesia similar to that produced by 50 mg meperidine.[20] Physostigmine is also useful in preventing and treating behavioral disturbances after propofol anesthesia.[21] Furthermore, physostigmine antagonizes myoclonus, implying that cholinergic hyperactivity contributes to the pathophysiology of this tremor.[22] All these observations suggest that the cholinergic system is likely to be among the mediators of shivering.

Cholinergic stimulation of the hypothalamic-pituitary-adrenal axis and adrenal medulla by physostigmine enhances secretion of arginine vasopressin, epinephrine, and norepinephrine. Because the hypothalamus is the dominant thermoregulatory controller in mammals, physostigmine-induced inhibition in this region may influence the incidence of shivering. Accordingly, we tested the hypothesis that physostigmine administration inhibits postanesthetic shivering. Its efficacy was compared with that of saline (negative control) and meperidine and clonidine (positive controls).

Methods

With institutional review board approval and written informed consent, we studied 60 patients (American Society of Anesthesiologists physical status 1 or 2) scheduled for elective ear, nose, or pharyngeal surgery. Patients were excluded when vasoconstrictor agents were required for surgery, $\alpha 2$-agonists were administered for long-term treatment, or symptoms and signs resembling Parkinson's disease were found. All patients were orally premedicated with midazolam (0.1 mg/kg) 45 min before anesthesia was induced. A cannula was inserted into a peripheral vein for infusion of Ringer's lactate solution and drug administration.

General anesthesia was induced using propofol (2 mg/kg) and fentanyl (1.5 μg/kg). Vecuronium (0.1 mg/kg) was administered to facilitate orotracheal intubation, but no additional muscle relaxants were given. Mechanical ventilation was adjusted to maintain end-tidal carbon dioxide tension at 36–38 mmHg (Normocap; Datex, Helsinki, Finland) using a fresh gas flow rate of 6 l/min. General anesthesia was maintained with isoflurane (1.5 ± 0.4% end-tidal concentration) and 70% nitrous oxide in oxygen. Patients were covered with warmed sheets during anesthesia but were not actively heated. Ambient temperature of the operating rooms and postanesthetic recovery area was maintained near 23°C.

Isoflurane and nitrous oxide administration was discontinued when surgery was complete. Nerve stimulation was used to confirm four of four twitches in response to train-of-four stimulation of the ulnar nerve at the wrist. After return of laryngeal reflexes (coughing during tracheal suctioning) and spontaneous ventilation $\geq 50\ ml \cdot kg^{-1} \cdot min^{-1}$, patients were randomly allocated to one of four groups (n = 15 each): (1) 0.04 mg/kg physostigmine, (2) saline control, (3) 0.5 mg/kg meperidine, or (4) 1.5 μg/kg clonidine. All test drugs were given intravenously using a double-blind protocol. The patients were extubated 5 min later and subsequently given oxygen *via* nasal prongs at a rate of 2 l/min.

Throughout surgery and the postanesthetic recovery period, we recorded systolic, mean, and diastolic arterial pressures (Dinamap; Critikon, Tampa, FL), heart rate, and oxygen saturation using a pulse oximeter (Nellcor, Hayward, CA). Core temperature was measured with a rectal probe inserted 10 cm past the anal sphincter (UM 3; Dräger, Lübeck, Germany). Postanesthetic shivering was graded visually by an anesthesiologist blinded to the drug administration and core tempera-

ture using a three-point scale (none, moderate, or severe).[3] Postoperative pain was assessed using a visual analog scale, in which a score of 0 mm indicated no pain and 100 mm identified maximal pain. A new unmarked scale was used for each evaluation.

Arousal state was assessed by patients' responses to the verbal command "Open your eyes and lift your arms." Absent or incomplete responses were graded as arousal state zero, and prompt and appropriate responses were graded as arousal state one. Postoperative nausea and vomiting was considered clinically important when vomiting was observed or nausea persisted for more than 10 min. Extubation was considered elapsed time zero. Postoperative pain was first evaluated 15 min after extubation, and then at 20, 25, 30, and 60 elapsed min. All other measures were recorded before and after extubation and subsequently at 5-min intervals for a period of 1 h.

Continuous, normally distributed variables were analyzed using one-way analysis of variance and Scheffé's F tests. Changes over time within each group were evaluated using repeated-measures analysis of variance and Scheffé's F tests. Shivering incidence was analyzed using a chi-squared test. Data are expressed as means $\pm$ SD; $P < 0.05$ was considered significant.

Results

Demographic data, duration of surgery, postoperative pain scores, and the time required to reach an arousal score of one were similar among groups. All patients awakened within 20 min of extubation, and arousal scores continued to increase throughout recovery. Core temperatures were also similar in each of the groups, and only mild hypothermia was observed. Oxygen saturation exceeded 94% in all patients and was similar in each group.

Six patients experienced nausea after treatment with physostigmine and three vomited in this group. Although the incidence of nausea and vomiting did not differ significantly from that in the other groups. Postoperative shivering was significantly reduced in patients given physostigmine (1 of 15, or 7%) compared with patients given saline (6 of 15, or 40%). No patient given clonidine or meperidine shivered. The incidence of shivering did not differ significantly in the patients given physostigmine, clonidine, and meperidine (table 1).

There were no clinically important differences in heart rate among the groups. Mean arterial blood pressure increased 10 min after administration of saline, physostigmine, or meperidine and subsequently remained elevated for 20 min. Mean arterial blood pressure was significantly greater 10 min after administration of physostigmine (126 $\pm$ 21 mmHg) than after saline (105 $\pm$ 33 mmHg). In contrast, mean arterial blood pressure remained constant after clonidine administration and was thus significantly lower than that in patients given saline (table 2).

Discussion

Shivering occurred in 40% of the patients when saline was administered but in only 7% after intravenous bolus administration of 0.04 mg/kg physostigmine. Cholinergic activation by physostigmine thus reduced the incidence of shivering as well as did clonidine or meperidine. Physostigmine may reduce postanesthetic shivering by a specific antishivering effect or, more likely, by increasing brain cholinergic neurotransmission and thus producing generalized thermoregulatory inhibition. Although our data do not distinguish these potential causes, previous work suggests that the primary mechanism is likely to be central.

Physostigmine antagonizes muscular hyperactivity in patients with essential myoclonus.[22] Other authors found that physostigmine stops the progression of cerebellar ataxia,[23] shortens esophageal electromechanical coupling time,[24] and normalizes manifestation of neuromuscular disorders.[25] Physostigmine administration thus reduces centrally mediated muscular hyperactivity, perhaps inhibiting the fraction of postanesthetic shivering that resembles clonus.[3]

Images produced by positron emission tomography identify the corpus striatum and the hypothalamus as the major brain region in which physostigmine is active.[26] Physostigmine activates hypothalamic adrenocortical receptors and enhances epinephrine and norepinephrine secretion.[27] Accordingly, physostigmine may also influence thermoregulatory processes and control normal thermoregulatory shivering at the level of the hypothalamus. Physostigmine reportedly produces analgesia, apparently by stimulating release of β-endorphins.[28] However, we found no significant analgesic effect from 0.04 mg/kg physostigmine during recovery from general anesthesia. This is consistent with previous studies in which 0.5–1.0 mg physostigmine given intravenously did not reduce pain in patients having neurosurgical procedures.[29] These data suggest that the

Table 1. Morphometric Characteristics, Anesthetic Variables, and the Incidence of Postoperative Pain and Shivering

	Physostigmine	Saline	Meperidine	Clonidine
Age (yr)	41 ± 14	39 ± 17	41 ± 17	42 ± 14
Sex (male/female)	9/6	9/6	10/5	7/8
Weight (kg)	76 ± 13	72 ± 12	71 ± 14	74 ± 16
Height (cm)	176 ± 11	170 ± 11	169 ± 9	173 ± 7
Duration of surgery (min)	63 ± 31	75 ± 32	78 ± 32	99 ± 41
Time to arousal score 1 (min)	11 ± 6	12 ± 6	13 ± 6	13 ± 7
T_c 15 min after extubation (°C)	35.8 ± 0.5	35.9 ± 0.6	35.9 ± 0.4	35.7 ± 0.4
Pain at 15 elapsed min (VAS)	35 ± 13	35 ± 22	38 ± 19	35 ± 19
Episodes of nausea/vomiting	6/3	3/1	3/3	3/2
Moderate shivering (%)	7	27	0	0
Severe shivering (%)	0	13	0	0
Overall shivering incidence (%)	7*	40	0*	0*

Data are mean ± SD.

VAS = visual analog score (mm); T_c = core temperature; elapsed time zero is extubation.

* $P < 0.05$ *versus* saline.

analgesic effects of physostigmine is limited, at least in the doses tested.

Shivering may be reduced by the sedative effects of the administered drugs. However, we found no differences in the awakening time after administration of physostigmine, meperidine, or clonidine, when compared with saline treatment. Physostigmine appears to be a safe, rapidly effective agent for reversing prolonged somnolence in parturients in whom meperidine, propiomazine, and scopolamine were used.[30] However, other authors found that physostigmine did not reverse benzodiazepine-induced sedation.[31] The antidotal effect of physostigmine (2 mg) after diazepam-nitrous oxide anesthesia concerning recovery scores was marginal,[32] and the degree of sedation did not change in patients recovering from midazolam-alfentanil-nitrous oxide anesthesia after intravenous administration of 2 mg physostigmine.[33] This is consistent with our findings, in which the awakening time was not shortened by intravenous physostigmine administration after isoflurane and nitrous oxide anesthesia.

Physostigmine administration slightly increased arterial blood pressure and heart rate for about 20 min after administration. This increase is consistent with most other studies,[34,35] although Breimer, *et al.*[33] observed heart rates up to 140 beats/min in several patients. The

Table 2. Systemic Hemodynamic Parameters before and after Bolus Administration of Physostigmine, Saline, Meperidine, or Clonidine

	Physostigmine		Saline		Meperidine		Clonidine	
	MAP	HR	MAP	HR	MAP	HR	MAP	HR
Baseline	98 ± 11	67 ± 10	95 ± 14	74 ± 15	95 ± 12	72 ± 13	99 ± 14	77 ± 10
5 min	111 ± 17*	85 ± 25*	101 ± 20	84 ± 24	109 ± 20	66 ± 8†	102 ± 25	82 ± 18
10 min	126 ± 21*†	97 ± 17*	105 ± 33	89 ± 21*	109 ± 17*	74 ± 10†	104 ± 19	82 ± 18
15 min	115 ± 17*	94 ± 17*	113 ± 20*	85 ± 15	108 ± 17*	79 ± 12	95 ± 9	80 ± 16
20 min	112 ± 10*	90 ± 19*	107 ± 15*	86 ± 19	109 ± 17*	81 ± 17	98 ± 8†	78 ± 13
25 min	106 ± 12	80 ± 14*	110 ± 16*	83 ± 17	105 ± 16*	88 ± 19	94 ± 14	78 ± 13
30 min	106 ± 20	78 ± 14*	102 ± 15	81 ± 16	105 ± 13*	83 ± 15	98 ± 14	78 ± 15
60 min	99 ± 19	71 ± 13	97 ± 12	79 ± 16	104 ± 15	78 ± 16	94 ± 9	71 ± 13

Data are mean ± SD.

MAP = mean arterial blood pressure (mmHg); HR = heart rate (beats/min).

* $P < 0.05$ *versus* baseline.

† $P < 0.05$ *versus* saline.

most common side effects of physostigmine are nausea and vomiting. We observed nausea in six patients after physostigmine administration, and three vomited. In contrast, three patients given saline became nauseated and only one vomited. Although these rates did not differ significantly, which is consistent with previous reports,[29] our data suggest that physostigmine may be somewhat more toxic in this regard than meperidine or clonidine.

A limitation of our protocol is that we examined only one dose of each drug. Both clonidine and meperidine have been studied extensively, and the effective doses are well established.[36,37] Consistent with previous experience, the doses we used were universally effective, and no shivering was observed in patients given either meperidine or clonidine. The dose of physostigmine we chose was similar to that used safely for other purposes in previous investigations.[38] Although this dose was effective in nearly all patients, it remains likely that higher doses would be more effective and, similarly, that lower doses would be less effective. It is unlikely, however, that physostigmine will be used routinely to treat postoperative shivering because clonidine and meperidine produce less hemodynamic and gastrointestinal toxicity. Furthermore, our purpose was simply to demonstrate the importance of cholinergic pathways in the control of shivering. Establishing the precise dose dependence thus was not necessary.

In conclusion, physostigmine reduced the incidence of shivering as did clonidine or meperidine. Cholinergic mechanisms thus appear to contribute to the genesis and control of postanesthetic shivering.

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