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Alfentanil Slightly Increases the Sweating Threshold and Markedly Reduces the Vasoconstriction and Shivering Thresholds

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Background: Hypothermia is common in surgical patients and victims of major trauma; it also results from environmental exposure and drug abuse. In most cases, hypothermia results largely from drug-induced inhibition of normal thermoregulatory control. Although opioids are given to a variety of patients, the thermoregulatory effects of opioids in humans remain unknown. Accordingly, the hypothesis that opioid administration impairs thermoregulatory control was tested.

Methods: Eight volunteers were studied, each on 3 days: (1) a target total plasma alfentanil concentration of 100 ng/ml, (2) control (no drug), and (3) a target alfentanil concentration of 300 ng/ml. Each day, skin and core temperatures were increased sufficiently to provoke sweating. Temperatures subsequently were reduced to elicit peripheral vasoconstriction

and shivering. Mathematical compensations were made for changes in skin temperature using the established linear cutaneous contributions to control of sweating (10%) and to vasoconstriction and shivering (20%). From the calculated thresholds (core temperatures triggering responses at a designated skin temperature of 34°C) and unbound plasma alfentanil concentrations, the individual concentration-response relationship was determined. The concentration-response relationship for all the volunteers was determined similarly using total alfentanil concentrations.

Results: In terms of unbound concentration, alfentanil increased the sweating threshold (slope = $0.021 \pm 0.016^\circ\text{C} \cdot \text{ng}^{-1} \cdot \text{ml}$; $r^2 = 0.92 \pm 0.06$). Alfentanil also significantly decreased the vasoconstriction (slope = $-0.075 \pm 0.067^\circ\text{C} \cdot \text{ng}^{-1} \cdot \text{ml}$; $r^2 = 0.92 \pm 0.07$) and shivering thresholds (slope = $-0.063 \pm 0.037^\circ\text{C} \cdot \text{ng}^{-1} \cdot \text{ml}$; $r^2 = 0.98 \pm 0.04$). In terms of total alfentanil concentration ($^\circ\text{C} \cdot \text{ng}^{-1} \cdot \text{ml}$), the sweating threshold increased according to the equation: threshold ($^\circ\text{C}$) = $0.0014[\text{alfentanil}] + 37.2$ ($r^2 = 0.33$). In contrast, alfentanil produced a linear decrease in the core temperature, triggering vasoconstriction: threshold ($^\circ\text{C}$) = $-0.0049[\text{alfentanil}] + 36.7$ ($r^2 = 0.64$). Similarly, alfentanil linearly decreased the shivering threshold: threshold ($^\circ\text{C}$) = $-0.0057[\text{alfentanil}] + 35.9$ ($r^2 = 0.70$).

Conclusions: The observed pattern of thermoregulatory impairment is similar to that produced by most general anesthetics: a slight increase in the sweating threshold and a substantial, linear decrease in the vasoconstriction and shivering thresholds. (Key words: Anesthesia. Opioid: alfentanil. Temperature. Thermoregulation: shivering; sweating; vasoconstriction.)

PERIOPERATIVE hypothermia is common¹ and associated with numerous complications, including myocardial ischemia,² decreased resistance to wound infections,³ and impaired coagulation.⁴ Hypothermia results from intraoperative heat loss and anesthetic-induced inhibition of normal thermoregulatory control.⁵ Hypothermia is common in other situations including major trauma,⁶ environmental exposure in the elderly,⁷ and drug abuse.⁸ Such hypothermia is associated with increased victim mortality⁶ and likely results in part from thermoregulatory impairment.

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Thermoregulatory responses are characterized by thresholds, the core temperatures triggering each protective response. The first autonomic response to heat stress is sweating, whereas the first autonomic response to cold is arteriovenous shunt vasoconstriction. Temperatures between these thresholds do not trigger thermoregulatory defenses and define the interthreshold range. Typical doses of all anesthetics so far tested increase the interthreshold range from $\approx 0.2^\circ\text{C}$ ⁹ to $3-5^\circ\text{C}$ by slightly increasing the sweating threshold and markedly decreasing the vasoconstriction threshold.¹⁰⁻¹⁴ General anesthesia also markedly decreases the shivering threshold.¹⁴

Opioids are among the most commonly administered anesthetic adjuvants; they are administered to patients in a variety of other circumstances, usually for relief of pain. However, the thermoregulatory effects of opioids in humans remain unknown. The thermoregulatory consequences of opioids cannot reliably be extrapolated from animal studies because of enormous species-to-species variability with these drugs.^{15,16} Accordingly, we tested the hypothesis that opioid administration increases the sweating threshold and decreases the vasoconstriction and shivering thresholds, thereby augmenting the interthreshold range. This is the first controlled study evaluating the thermoregulatory effects of opioid administration in humans.

Methods

With institutional review board approval and written informed consent, we studied ten male volunteers. Two were eliminated from the study after experiencing nausea on the first study day. Morphometric characteristics of the remaining eight were as follows: age 29 ± 4 yr; height 177 ± 3 cm; and weight 69 ± 4 kg. The percentage of body fat was 19 ± 4 (Futrex, Hagerstown, MD). None was obese, was taking medication, or had a history of thyroid disease, dysautonomia, or Raynaud's syndrome.

Volunteers were each evaluated on 3 days: (1) a target total alfentanil plasma concentration of 100 ng/ml, (2) a control day when no drug was given, and (3) a target alfentanil plasma concentration of 300 ng/ml. The treatment order was consistent, and at least 2 weeks were allowed between the alfentanil days to minimize the effects of tolerance. All studies were conducted in July 1994.

On each day, volunteers were warmed until sweating was observed and then cooled gradually until vasocon-

striction and shivering occurred. Core-temperature response thresholds were determined by arithmetically compensating for alterations in skin temperature using previously determined cutaneous contributions to thermoregulatory control.¹⁴

Treatment Protocol

The volunteers fasted 8 h before arriving at the laboratory. They were minimally clothed and rested supine in a $22-23^\circ\text{C}$ room during the protocol. Studies were scheduled so that thermoregulatory responses were triggered at similar times each day.

A catheter was inserted in a left forearm vein for fluid and alfentanil administration. A 14-G catheter was inserted in a right antecubital vein for blood sampling. Alfentanil was administered using a pump (Ohmeda 9000, Ohmeda, Steeton, England) programmed to target alfentanil blood concentrations of 100 and 300 ng/ml using a modification of the method of Kruger-Thiemer¹⁷ and published data.¹⁸

Throughout the protocol, arms were protected from active warming and cooling to avoid locally mediated vasomotion.¹⁹ However, all other skin below the neck was similarly manipulated. After 15 min of alfentanil administration, skin and core temperatures were increased gradually with a Bair Hugger forced-air warmer (Augustine Medical, Eden Prairie, MN) and circulating-water mattress (Cincinnati Sub-Zero, Cincinnati, OH) until significant sweating was achieved. Skin and core temperatures then were decreased gradually, using the circulating-water mattress and a prototype forced-air cooler (Augustine Medical).²⁰ The study ended each day when shivering was detected. Temperature changes were restricted to $\leq 3^\circ\text{C}/\text{h}$ because this rate is unlikely to trigger dynamic thermoregulatory responses.⁹

Measurements

Core temperature was recorded from the tympanic membrane (Mallinckrodt, St. Louis, MO).¹⁰ Mean skin-surface temperature was calculated from measurements at 15 area-weighted sites.^{5,21} Temperatures were recorded at 5-min intervals from thermocouples connected to Iso-Thermex thermometers having an accuracy of 0.1°C (Columbus Instruments, Columbus, OH).

Sweating was quantified continuously on the left upper chest using a ventilated capsule.^{11,13} A sustained sweating $> 40 \text{ g} \cdot \text{m}^{-2} \cdot \text{h}^{-1}$ was considered significant.¹⁴ Absolute right middle fingertip blood flow was quantified using venous-occlusion volume plethysmography

at 5-min intervals.²² A sustained blood flow to $< 0.25 \text{ ml}/\text{min}$ was considered vasoconstriction.

Shivering was evaluated using a Deltatrac metabolic monitor (Linda, CA). The system was used to measure energy expenditure and measurements were averaged over 5 min. Shivering was sustained for 5 min. Shivering was considered significant if the increase in energy expenditure was $> 10\%$ above the resting level. The server was blinded to treatment and temperatures.

Peripheral venous blood was drawn for alfentanil concentration, and at the time of vasoconstriction, and shivering for metabolic measurements. Each study day, alfentanil was added to 1 ml of blood sample and the resulting concentration was determined using the Micro-partition System (Amicon, Denver, CO). The assay was linear to at least $10 \mu\text{g}/\text{ml}$, and the limit of detection was $2 \text{ ng}/\text{ml}$ with a $200 \mu\text{g}/\text{ml}$ day coefficient of variation of 10% .

Pupil diameter and light reflex were measured with an infrared pupillometer (Optics, Buckinghamshire, UK). The pupillometer was programmed to provide a 0.5-s exposure of green light and scan the pupil every 2 s from the beginning of the study. Pupil size during the study was identified the reflex amplitude was maintained near 150 lux , and covered during the measurements. Heart rate and blood pressure were measured at 5-min intervals. End-tidal P_{CO_2} was measured with a catheter inserted into one nostril and sampled by this monitor with a Deltatrac.

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at 5-min intervals.²² A sustained decrease in fingertip blood flow to <0.25 ml/min identified significant vasoconstriction.

Shivering was evaluated using oxygen consumption (Deltatrac metabolic monitor, SensorMedics, Yorba Linda, CA). The system was used in canopy mode, and measurements were averaged over 1-min intervals and recorded every 5 min. An increase in oxygen consumption sustained for 5 min identified significant shivering; this increase was identified by an observer blinded to treatment and core and skin temperatures.

Peripheral venous blood was sampled before drug administration, and at the time of sweating, vasoconstriction, and shivering for measurement of alfentanil blood concentration. Each study day, 200–300 ng alfentanil was added to 1 ml of plasma from the initial blood sample and the resulting mixture centrifuged using the Micro-partition System MPS-1 with YM-T membrane (Amicon, Denver, CO) for 30 min. We assumed, as have others,²³ that protein binding remained constant over the hours of study. Consequently, the unbound drug fractions was determined once each study day. The ultrafiltrate and plasma samples were stored at -20°C until analysis by high-performance liquid chromatography, using a modification of a previously described technique.²⁴ This assay is linear to at least $10\text{ }\mu\text{g/ml}$, with a detection limit of 2 ng/ml with a $200\text{ }\mu\text{l}$ injection, and within-day coefficient of variation of 4.1% ($n = 6$) at 250 ng/ml .

Pupil diameter and light-reflex amplitude correlate well with opioid effect.²⁵ Consequently, pupillary responses were used to evaluate pharmacodynamic effects of alfentanil. An infrared pupillometer (Fairville Medical Optics, Buckinghamshire, England) was used to measure the pupillary response. The pupillometer was programmed to provide a $0.5\text{-s } 130\text{ candela/m}^2$ pulse of green light and scan the pupil at a rate of 10 Hz for 2 s from the beginning of the light stimulus. The reduction in pupil size during the 2 s of light exposure identified the reflex amplitude. Ambient light was maintained near 150 lux , and the left eye was kept covered during the measurements.

Heart rate and blood pressure was determined oscillometrically at 5-min intervals (Modulus CD, Ohmeda, Salt Lake City, UT). End-tidal P_{CO_2} was measured from a catheter inserted into one nostril (Rascal, Ohmeda); gas sampled by this monitor was returned to the Deltatrac.

Data Analysis

Hemodynamic responses and ambient temperature and humidity on each study day first were averaged within each volunteer; the resulting values were averaged among volunteers. Results for each study day were compared using repeated-measures analysis of variance and Scheffé's F tests. Mean skin temperatures, end-tidal P_{CO_2} , alfentanil blood concentrations, the unbound alfentanil fraction, and pupillary responses at each threshold were similarly compared. Results are presented as mean \pm SD; $P < 0.01$ was considered statistically significant.

The cutaneous contribution to sweating²⁶ and to vasoconstriction and shivering²⁷ is linear. We thus used measured skin and core temperatures in degrees Celsius at each threshold to calculate the core-temperature threshold that would have been observed had skin been maintained at a single designated temperature:

$$T_{\text{Core(calculated)}} = T_{\text{Core}} + \left(\frac{\beta}{1 - \beta} \right) [T_{\text{Skin}} - T_{\text{Skin(designated)}}],$$

where the fractional contribution of mean skin temperature to the threshold was termed β . $T_{\text{Core(calculated)}}$ equals the measured core temperature, T_{Core} , plus a small correction factor consisting of $\beta/(1-\beta)$ multiplied by the difference between actual (T_{Skin}) and designated [$T_{\text{Skin(designated)}}$] skin temperatures. We previously described the derivation, limitations, and validation of this equation.¹⁴

We used a β of 0.1 for sweating²⁶ and a β of 0.2 for vasoconstriction and shivering.²⁷ The designated skin temperature was set at 34°C , a typical intraoperative value. From the calculated core-temperature thresholds at each dose, unbound alfentanil concentration-response curves for the sweating, vasoconstriction, and shivering thresholds were determined using linear regression. The average slopes and correlation coefficients (r^2) for the eight volunteers were computed from these values. Additionally, a single regression for each response was determined from the mean data from all eight volunteers using total plasma concentration.

Results

Volunteers typically were mildly sedated when the target total plasma alfentanil concentration was 100 ng/ml and deeply sedated when the target concentration was 300 ng/ml . Most required verbal reminders to breathe at the lower target alfentanil concentration,

Table 1. Environmental and Anesthetic Data, Total Plasma Alfentanil Concentrations, and Unbound Alfentanil Fraction

	Control	100 ng/ml	300 ng/ml
Ambient temperature (°C)	22.4 ± 0.6	22.6 ± 0.5	22.9 ± 0.3
Relative humidity (%)	37 ± 5	38 ± 2	35 ± 5
Mean arterial blood pressure (mmHg)	101 ± 9	88 ± 5	85 ± 7
Heart rate (beats/min)	68 ± 12	64 ± 7	70 ± 8
End-tidal P _{CO₂}	38 ± 3	41 ± 2	43 ± 4
[Alfentanil] at sweating (ng/ml)	—	99 ± 21	292 ± 48
[Alfentanil] at vasoconstriction (ng/ml)	—	100 ± 18	285 ± 43
[Alfentanil] at shivering (ng/ml)	—	97 ± 18	289 ± 45
Unbound alfentanil (%)	—	7 ± 2	7 ± 2

On the control day, no alfentanil was given; 100- and 300-ng/ml total blood alfentanil concentrations were targeted on the other 2 days. There were no clinically important differences in ambient temperature, relative humidity, heart rate, blood pressure, or end-tidal P_{CO₂} on the 3 study days. By design, the blood alfentanil concentrations differed significantly on each of the treatment days. Values are mean ± SD.

and all required frequent reminders at the higher concentration.

There were no clinically important differences in ambient temperature, relative humidity, heart rate, blood pressure, or end-tidal P_{CO₂} on the 3 study days. By design, blood alfentanil concentrations differed significantly on each of the treatment days (table 1).

The interthreshold range was 0.4 ± 0.2°C on the control day, increased significantly to 1.1 ± 0.2°C when the target total plasma alfentanil concentration was 100 ng/ml, and further increased significantly to 2.2 ± 0.8°C when the target was 300 ng/ml. The va-

soconstriction-shivering (difference between the respective thresholds) range on the control day was 0.9 ± 0.3°C and increased only slightly during alfentanil administration. Pupil size and reflex amplitude decreased progressively and significantly as alfentanil concentration was augmented; however, there were no significant differences at the thresholds for each target concentration (table 2).

Unbound plasma alfentanil significantly decreased the core temperature, triggering vasoconstriction (slope = -0.075 ± 0.067°C · ng⁻¹ · ml; r² = 0.92 ± 0.07) and shivering (slope = -0.063 ± 0.037°C · ng⁻¹ · ml; r² =

Table 2. Mean Skin Temperatures, Core Temperatures, Calculated Thresholds (Assuming 34°C Skin Temperature), and Pupillary Responses

		Control	100 ng/ml	300 ng/ml
Sweating	Mean skin temperature (°C)	36.3 ± 0.4	36.5 ± 0.5	36.8 ± 0.3
	Core temperature (°C)	36.9 ± 0.2	37 ± 0.2	37.3 ± 0.2
	Threshold temperature (°C)	37.2 ± 0.2	37.3 ± 0.2	37.6 ± 0.3
	Pupil diameter (mm)	5.9 ± 0.9	3.6 ± 1.2	1.9 ± 0.3
	Reflex amplitude (mm)	2.2 ± 0.4	1.3 ± 0.6	0.5 ± 0.2
Vasoconstriction	Mean skin temperature (°C)	33.4 ± 0.8	32.5 ± 1.0	31.2 ± 1.7
	Core temperature (°C)	36.9 ± 0.2	36.6 ± 0.2	36.2 ± 0.5
	Threshold temperature (°C)	36.8 ± 0.3	36.2 ± 0.3	35.4 ± 0.8
	Pupil diameter (mm)	5.9 ± 0.9	3.9 ± 1.0	2.2 ± 0.4
	Reflex amplitude (mm)	2.3 ± 0.5	1.3 ± 0.4	0.4 ± 0.1
Shivering	Mean skin temperature (°C)	30 ± 1.3	29.7 ± 1.1	28.2 ± 1.7
	Core temperature (°C)	36.9 ± 0.2	36.5 ± 0.3	35.8 ± 0.6
	Threshold temperature (°C)	35.9 ± 0.4	35.4 ± 0.3	34.3 ± 0.8
	Pupil diameter (mm)	5.8 ± 0.8	3.8 ± 1.0	1.9 ± 0.4
	Reflex amplitude (mm)	2.0 ± 0.4	1.4 ± 0.4	0.5 ± 0.1

Mean skin and core temperatures at sweating, vasoconstriction, and shivering, and the thresholds calculated from these values at each target total plasma alfentanil concentration. Pupillary responses also are shown. Pupil size and reflex amplitude decreased progressively and significantly as alfentanil concentration was augmented; however, there were no significant differences among the thresholds at each target concentration. Values are mean ± SD.

0.98 ± 0.04). In contrast, increased concentration augmented the sweating slightly: slope = 0.021 ± 0.016°C · ng⁻¹ · ml (± 0.06). The amount of inhibition among volunteers; however, responses curves were linear in each case. Figure 2 shows the regression lines of total plasma alfentanil concentration versus the thresholds calculated using the mean data from

Discussion

Alfentanil increased the thresholds for vasoconstriction and shivering, and reduced the thresholds for sweating.

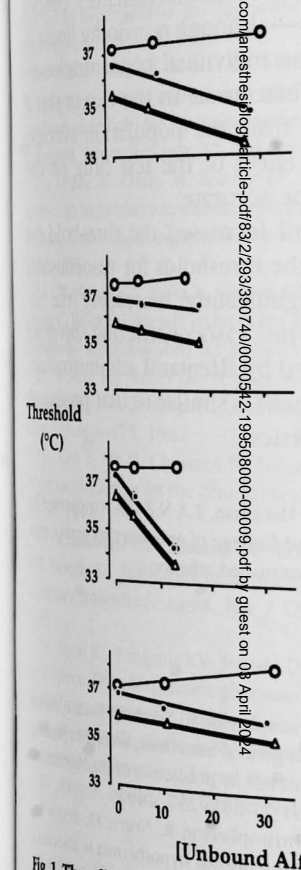


Fig. 1. The effect of increasing unbound alfentanil concentration on the core temperature (open circles), vasoconstriction (filled circles), and shivering (filled triangles) in eight volunteers. Unbound plasma concentration, line slopes: core temperature, -0.063 ± 0.037°C · ng⁻¹ · ml, respectively; vasoconstriction and shivering thresholds increased only slightly (0.021 ± 0.016°C · ng⁻¹ · ml, respectively). The thresholds (at a designated skin temperature) were calculated from measured skin and

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0.98 ± 0.04). In contrast, increasing alfentanil blood concentration augmented the sweating threshold only slightly: slope = $0.021 \pm 0.016^\circ\text{C} \cdot \text{ng}^{-1} \cdot \text{ml}$ ($r^2 = 0.92 \pm 0.06$). The amount of inhibition varied considerably among volunteers; however, the concentration-responses curves were linear in each (fig. 1).

Figure 2 shows the regressions for each threshold in terms of total plasma alfentanil concentration, calculated using the mean data from all volunteers.

Discussion

Alfentanil increased the threshold for sweating and reduced the thresholds for vasoconstriction and shivering.

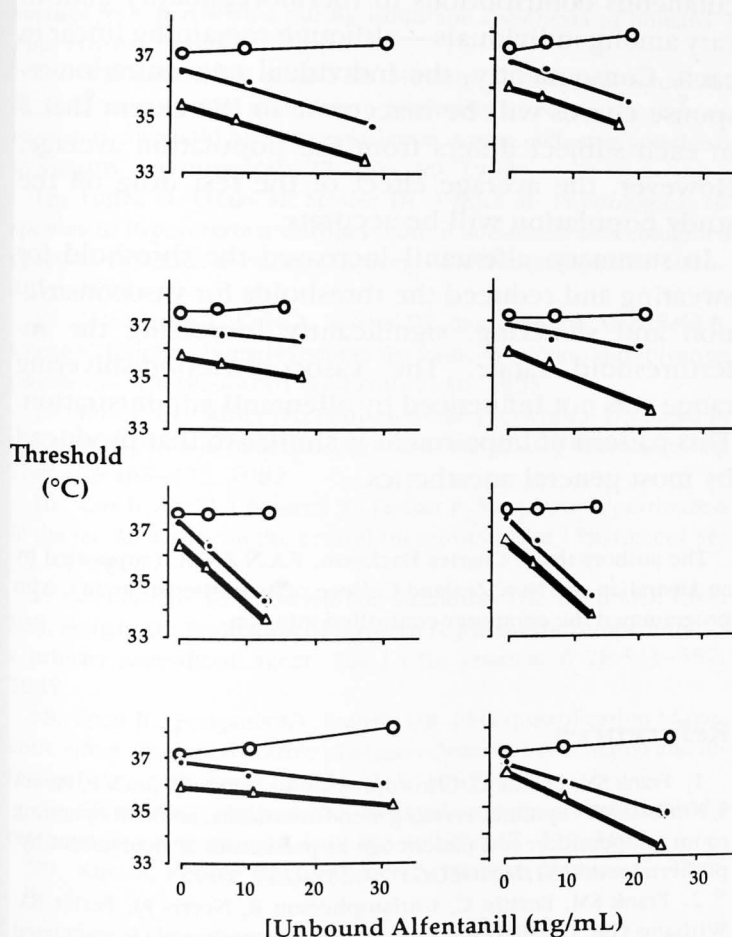


Fig. 1. The effect of increasing unbound plasma alfentanil concentration on the core temperatures triggering sweating (open circles), vasoconstriction (filled circles), and shivering (open triangles) in eight volunteers. Unbound alfentanil, up to 30 ng/ml plasma concentration, linearly reduced both the vasoconstriction and shivering thresholds by 0.075 ± 0.067 and $0.063 \pm 0.037^\circ\text{C} \cdot \text{ng}^{-1} \cdot \text{ml}$, respectively. The sweating threshold increased only slightly ($0.021 \pm 0.016^\circ\text{C} \cdot \text{ng}^{-1} \cdot \text{ml}$). All the thresholds (at a designated skin temperature of 34°C) were calculated from measured skin and core temperatures.

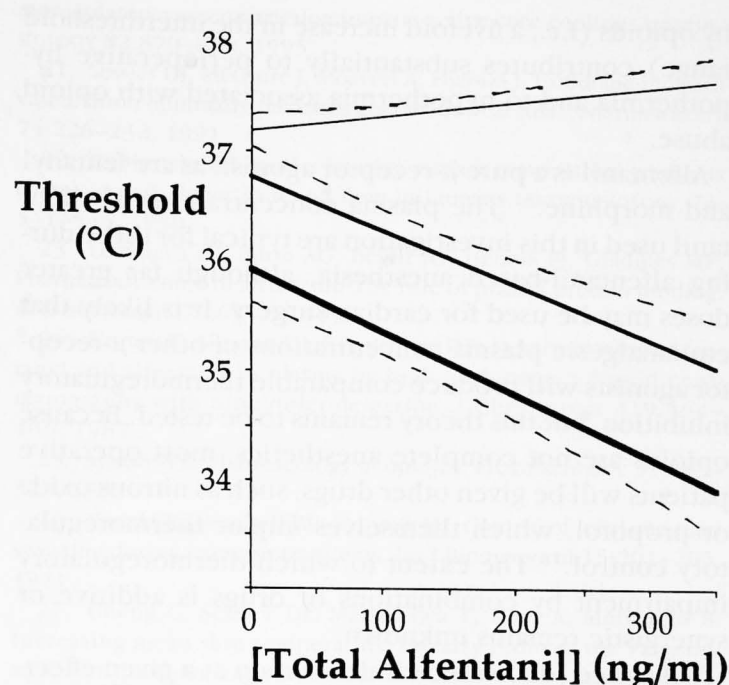


Fig. 2. The sweating threshold increased as a function of total plasma alfentanil concentration: thin upper regression, threshold ($^\circ\text{C}$) = $0.0014[\text{alfentanil}(^\circ\text{C} \cdot \text{ng}^{-1} \cdot \text{ml})] + 37.2$ ($r^2 = 0.33$). In contrast, alfentanil produced a linear decrease in the core temperature triggering vasoconstriction: middle regression, threshold ($^\circ\text{C}$) = $-0.0049[\text{alfentanil}(^\circ\text{C} \cdot \text{ng}^{-1} \cdot \text{ml})] + 36.7$ ($r^2 = 0.64$). Similarly, alfentanil linearly decreased the shivering threshold: thick lower regression: threshold ($^\circ\text{C}$) = $-0.0057[\text{alfentanil}(^\circ\text{C} \cdot \text{ng}^{-1} \cdot \text{ml})] + 35.9$ ($r^2 = 0.70$). Dashed lines indicate 95% confidence intervals. These regression slopes differ from those reported in figure 1 because they were calculated from the mean values in all volunteers rather than individuals and because they were calculated on the basis of total rather than unbound plasma alfentanil concentration.

ering, significantly increasing the interthreshold range. This pattern of thermoregulatory impairment is similar to that produced by isoflurane,^{10,11} enflurane,^{12,13} and propofol.¹⁴

Intraoperative hypothermia results initially from a core-to-peripheral redistribution of body heat that occurs when anesthetics impair tonic thermoregulatory vasoconstriction.⁵ Subsequently, core temperature decreases linearly because heat loss exceeds production.²⁸ Finally, a core-temperature plateau results from re-emergence of thermoregulatory vasoconstriction, which decreases cutaneous heat loss²⁹ and constrains metabolic heat to the core thermal compartment.³⁰ In most cases, anesthetic-induced inhibition of thermoregulatory control—and subsequent reemergence of control—contributes more to observed temperature perturbations than cold exposure *per se*. It is thus likely that marked impairment of thermoregulatory control

by opioids (*i.e.*, a fivefold increase in the interthreshold range) contributes substantially to perioperative hypothermia and to hypothermia associated with opioid abuse.

Alfentanil is a pure μ -receptor agonist, as are fentanyl and morphine.³¹ The plasma concentrations of alfentanil used in this investigation are typical for those during alfentanil-based anesthesia, although far greater doses may be used for cardiac surgery. It is likely that equianalgesic plasma concentrations of other μ -receptor agonists will produce comparable thermoregulatory inhibition, but this theory remains to be tested. Because opioids are not complete anesthetics, most operative patients will be given other drugs, such as nitrous oxide or propofol, which themselves impair thermoregulatory control.¹⁴ The extent to which thermoregulatory impairment by combinations of drugs is additive or synergistic remains unknown.

Tolerance (decreased clinical action at a given effect-site concentration) is a characteristic feature of opioids. Development of tolerance is both dose- and time-dependent but is similar with opioids of differing potencies.³² The amount of alfentanil required when the target plasma concentration was 100 ng/ml was far less than at the larger concentration: Not only was the drug administered at about one-third the rate, but it was given for about half the time because smaller temperature deviations were required to trigger thermoregulatory responses. We minimized the chance of developing significant tolerance by administering the smaller dose first, rather than randomizing treatment order. The time required to recover normal pharmacodynamic responses after several hours of opioid administration remains unclear. However, the 2 weeks we allowed between the smaller and larger target alfentanil concentrations should have been adequate.³³

Acute tolerance can develop within hours in animals,³⁴ but it remains unknown whether tolerance develops equally rapidly in humans. We could not decrease alfentanil exposure (to minimize tolerance) without excessively increasing the rate of skin and core temperature changes.³⁵ Nor was it practical to randomly assign volunteers to initial warming or cooling (to minimize a systematic effect of tolerance): Because the cold-response thresholds were so reduced, rewarming to sweating would excessively prolong the study. Consequently, we used pupillary responses to evaluate opioid effect. As expected, pupillary responses were markedly reduced by increasing opioid concentrations.²⁵ However, there were no significant differences

among the three thresholds tested on each study day. These results suggest that acute tolerance did not decrease opioid effect over the hours required for each study day.

An obvious major limitation of our current protocol is that it assumes constant and linear cutaneous contributions to thermoregulatory control during drug administration. This assumption seems to be valid, at least for propofol.¹⁴ However, the method also assumes that the fractional contribution of skin temperature to thermoregulatory control (β) is comparable for different drugs. Although it is probable that the fractional contribution of skin and core temperatures remains nearly constant under various circumstances, there is currently no assurance that the values of β used in this protocol were correct. An additional limitation is that specific cutaneous contributions to thermoregulatory control vary among individuals—although remaining linear in each. Consequently, the individual concentration-response curves will be inaccurate to the extent that β in each subject differs from the population average. However, the average effect of the test drug on the study population will be accurate.

In summary, alfentanil increased the threshold for sweating and reduced the thresholds for vasoconstriction and shivering, significantly increasing the interthreshold range. The vasoconstriction-shivering range was not influenced by alfentanil administration. This pattern of impairment is similar to that produced by most general anesthetics.

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