

Nefopam and Alfentanil Additively Reduce the Shivering Threshold in Humans whereas Nefopam and Clonidine Do Not

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Background: Induction of therapeutic hypothermia is often complicated by shivering. Nefopam reduces the shivering threshold with minimal side effects. Consequently, nefopam is an attractive component for induction of therapeutic hypothermia. However, nefopam alone is insufficient; it will thus need to be combined with another drug. Clonidine and alfentanil each reduce the shivering threshold. This study, therefore, tested the hypothesis that nefopam, combined either with clonidine or alfentanil, synergistically reduces the shivering threshold.

Methods: For each combination, ten volunteers were studied on 4 days. Combination 1: (1) control (no drug); (2) nefopam (100 ng/ml); (3) clonidine (2.5 µg/kg); and (4) nefopam plus clonidine (100 ng/ml and 2.5 µg/kg, respectively). Combination 2: (1) control (no drug); (2) nefopam (100 ng/ml); (3) alfentanil (150 ng/ml); and (4) nefopam plus alfentanil (100 ng/ml and 150 ng/ml, respectively). Lactated Ringer's solution (approximately 4°C) was infused to decrease core temperature. Mean skin temperature was maintained at 31°C. The core temperature that increased oxygen consumption to more than 25% of baseline identified the shivering threshold.

Results: With nefopam and clonidine, the shivering thresholds were significantly lower than on the control day. The shivering threshold decreased significantly less than would be expected on the basis of the individual effects of each drug ($P = 0.034$). In contrast, the interaction between nefopam and alfentanil on shivering was additive, meaning that the combination reduced the shivering threshold as much as would be expected by the individual effect of each drug.

Conclusions: Nefopam and alfentanil additively reduce the shivering threshold, but nefopam and clonidine do not.

NUMEROUS animal data suggest that mild hypothermia is protective against cerebral ischemia, especially stroke.^{1,2} Mild hypothermia improves neurologic outcomes in survivors of out-of-hospital cardiac arrest.^{3,4} In acute stroke patients, body temperature is associated with initial

stroke severity, infarct size, and mortality,⁵ and admission hypothermia is an independent predictor of good short-term outcome.⁶ Hypothermia also reduces intracranial pressure, and might improve recovery from catastrophic strokes resulting from middle cerebral artery occlusion.⁷ And finally, magnetic resonance imaging examination suggests a trend for decreased infarct growth in patients treated with moderate hypothermia.⁸

However, thermoregulatory defenses are usually well maintained, even in stroke victims.⁹ Consequently, it is difficult to induce hypothermia in these patients. Furthermore, shivering induces thermal discomfort,¹⁰ along with sympathetic nervous system activation¹¹ and consequent tachycardia and hypertension.¹² Routine clinical use of therapeutic hypothermia thus depends on the development of drugs that inhibit cold defenses. Many such drugs are already known, but they are all anesthetics^{13,14} or sedatives,^{15,16} and most produce substantial respiratory toxicity in therapeutic doses.

Most stroke patients are not mechanically ventilated or even maintained in critical care units. Any generally useful drug or drug combination will thus have to produce minimal respiratory depression. Combinations of various drugs have previously been tested in an effort to achieve thermal tolerance without major adverse effects.^{17,18} When meperidine and dexmedetomidine are combined, for example, they additively reduce shivering threshold.¹⁷ The combination of buspirone and meperidine is even more promising because it produces a synergistic reduction in shivering.^{17,18} Meperidine, though, causes both sedation and respiratory depression. Furthermore, its metabolite—normeperidine—promotes seizures. The search continues for a drug or drug combination that defeats shivering without excessive sedation, respiratory depression, or hemodynamic instability.

Nefopam is a centrally acting analgesic^{19,20} that is structurally related to orphenadrine and diphenhydramine.¹⁹ Nefopam reduces the shivering threshold without having any discernable effect on the vasoconstriction or sweating thresholds.²¹ *In vitro* and *in vivo* studies indicate that nefopam's properties are mediated by inhibition of catecholamine reuptake.²² Nefopam also directly interacts with α_2 -adrenoceptors.²² And finally, nefopam is a noncompetitive *N*-Methyl-D-Aspartate receptor antagonist.²³ Each of these receptors also mediates thermoregulatory responses.²⁴ Nefopam does not have sedative and hemodynamic effects as do α_2 agonists, nor does it cause respiratory depression as do opioids.²⁵

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Consequently, nefopam is an attractive component of a pharmacologic strategy for induction of therapeutic hypothermia. The difficulty is that nefopam alone is insufficiently potent because even fairly high doses do not lower the shivering threshold (triggering core temperature) to target core temperatures (usually 33 to 34°C) needed for therapeutic hypothermia. From previous data, a blood concentration of 200 ng · ml⁻¹ of nefopam would be necessary to achieve the target temperature in almost all the patients. That corresponds to the administration of 80 to 90 mg of nefopam in adults — a dose that is almost four times the usual 20 mg given for postoperative analgesia. Even though these doses have been previously administered without deleterious consequences,²⁶ and even though they are far from toxic,²⁷⁻²⁹ they probably are not appropriate for routine use. To facilitate induction of therapeutic hypothermia, nefopam will thus have to be combined with another drug.

Among the drugs known to lower the shivering threshold, most act *via* catecholaminergic pathways, opiate receptors, or both. Drugs from these therapeutic classes are thus obvious candidates for combination with nefopam. Clonidine is an α_2 agonist, and alfentanil is a pure μ agonist. Both lower the shivering threshold.^{15,30} Before introducing a new combination into clinical practice, it is thus of considerable interest to consider the extent to which the antishivering effect of nefopam is augmented or diminished by combining with an α_2 agonist such as clonidine or with a pure μ agonist like alfentanil. We therefore asked whether the interactions were antagonistic, additive, or synergistic. Specifically, we tested the hypothesis that the combination of nefopam and clonidine and the combination of nefopam and alfentanil synergistically reduce the shivering threshold.

Materials and Methods

With approval from the Ethics Committee of Hôpital Ambroise Paré (Boulogne-Billancourt, France) and informed consent, we studied 15 healthy male volunteers. None was obese, taking medication, or had a history of thyroid disease, dysautonomia, or Raynaud's syndrome.

Protocol

The volunteers had a light breakfast and refrained from caffeine for at least 8 h before the study. To avoid circadian fluctuations, studies were scheduled so that thermoregulatory responses were triggered at similar times on each of the study days. During the studies, the volunteers rested supine. They were minimally clothed, and ambient temperature was maintained near 20°C.

The study was conducted in a single-blind fashion. The volunteers were studied on four or six randomly-assigned days, each separated by at least 48 h: (1) control, no drug; (2) nefopam at a target plasma concentration of 0.1 μ g/ml (Nefopam); (3) clonidine 2.5 μ g/kg IV (Clonidine); (4) clonidine 2.5 μ g/kg IV and nefopam at a target plasma concentration of 0.1 μ g/ml combination (Combi 1); (5) alfentanil at a target plasma concentration of 0.15 μ g/ml (Alfentanil); (6) nefopam and alfentanil combination at target concentrations of 0.1 μ g/ml and 0.15 μ g/ml, respectively (Combi 2).

An 18-cm-long 4.5-French catheter (Vygon, Ecoen, France) was introduced through an antecubital vein. This catheter was used for cold-fluid infusion and blood sampling. A venous catheter was inserted into the other arm for drug administration. Throughout the study period, mean skin temperature was maintained at 30°C by adjusting the ambient temperature.

Thermal manipulation began 30 min after the study drugs were started. Lactated Ringer's solution cooled to 4°C was infused at rates sufficient to decrease tympanic membrane temperature 1 to 2°C/h. Fluid was given until the shivering threshold was identified or a total of 70 ml/kg was given. A pediatric forced-air cover connected to a warmer (Warmtouch, Mallinckrodt, Inc., St. Louis, MO) was rolled up around the arm used for cold solution infusion.

Nefopam and alfentanil were given intravenously *via* an Orchestra[®] Base A (Fresenius Vial Inc, Brezins, France) connected to a local software written in Visual Basic 5.0 (Microsoft, Redmond, MA). The nefopam infusion profile was based on published pharmacokinetic data³¹ and was designed to provide a time to peak plasma concentrations of 20 min with a mean elimination half-life of 240 min. This dosing scheme was intended to rapidly achieve therapeutic concentrations, minimize side effects during the initial phase, and maintain a therapeutic level throughout the study. The infusion rates for the target plasma levels of alfentanil were determined using Shafer's body surface adjusted pharmacokinetic modeling program, adjusted for age, sex, and weight.||

The choice for drug doses was based on two points: (1) achieving at least a 1°C decrease of shivering threshold; (2) avoiding toxicity. From previous data, a concentration of 0.1 μ g · ml⁻¹ of nefopam was chosen to obtain around a 1.5°C decrease of shivering threshold in our volunteers. For alfentanil, a target blood concentration of 150 ng/ml was chosen from published data.¹⁵ With this dose, a 1°C shivering threshold decrease was expected with only minor respiratory depression and minimal sedation.

Pharmacokinetic parameters of clonidine disposition could be described by a two-compartment open model with a rapid distribution phase followed by a slow elimination phase.³² Under these conditions, 30 min after bolus administration, plasmatic concentrations of clonidine remain almost unchanged over the 90-120 min neces-

|| STANPUMP program. Available at: <http://www.opentci.org>; accessed November 5, 1996.

sary for triggering shivering and maintenance of clonidine perfusion is unnecessary. The dose of 2.5 $\mu\text{g}/\text{kg}$ of clonidine was chosen from previously published data; 75 μg of clonidine given in volunteers weighing around 74 kg decreases shivering threshold by almost 0.5°C.³⁰ Because it decreases shivering threshold in a dose-dependent manner,³³ a clonidine dose of 2.5 μg was chosen to obtain a 1°C decrease of the shivering threshold.

Measurements

Heart rate and pulse-oximeter saturation were monitored continuously. Arterial pressure was determined oscillometrically at the ankle at 10-min intervals, but it was also recorded at the shivering threshold. Oxygen consumption and carbon dioxide production were measured by a DeltaTrac metabolic monitor (Datex-Ohmeda, Helsinki, Finland). The system was used in canopy-mode with measurements averaged over 1-min intervals and recorded every minute.

Core temperature was measured at the tympanic membrane. The aural probe was inserted until the patients felt the thermocouple touch the tympanic membrane; appropriate placement was confirmed when they easily detected a gentle rubbing of the attached wire. The probe was then securely taped in place, the aural canal was occluded with cotton, and the external ear was covered with a gauze bandage. Mean skin temperature (T_{Skin}) was calculated from ten sites by using the formula³⁴:

$$T_{\text{Skin}}(^{\circ}\text{C}) = 0.06 \cdot T_{\text{Forehead}} + 0.09 \cdot T_{\text{Arm}} \\ + 0.06 \cdot T_{\text{Forearm}} + 0.045 \cdot T_{\text{Hand}} + 0.19 \cdot T_{\text{Back}} \\ + 0.095 \cdot T_{\text{Chest}} + 0.095 \cdot T_{\text{Abdomen}} + 0.19 \cdot T_{\text{Thigh}} \\ + 0.115 \cdot T_{\text{Calf}} + 0.06 \cdot T_{\text{Foot}}$$

All temperatures were measured using Ellab thermometers and probes (Ellab, Inc., Copenhagen, Denmark); they were electronically recorded at 10-s intervals until the end of the study.

Thermoregulatory vasoconstriction was determined by estimating fingertip blood flow, which was evaluated using forearm minus fingertip, skin-surface temperature gradients.³⁵ Gradients exceeding 0°C were indicative of vasoconstriction because this gradient corresponds to onset of the core-temperature plateau.³⁶ As in numerous previous studies, shivering was evaluated by a blinded observer and confirmed by a sustained increase in oxygen consumption to 25% above the baseline.

Sedation was evaluated by using the responsiveness component of a modified Observer's Assessment of Alertness/Sedation score (table 1). Thermal comfort was assessed at each threshold with a 100-mm-long visual analog scale, with 50 mm defined as thermal comfort, 0 mm as the most intense imaginable sensation of cold, and 100 mm being the most intense imaginable sensa-

Table 1. Responsiveness Component of a Modified Observer's Assessment of Alertness/Sedation Scale

Score	Responsiveness
5	Responds readily to name spoken in normal tone
4	Lethargic response to name spoken in normal tone
3	Responds only after name is spoken loudly and/or repeatedly
2	Responds only after mild prodding or shaking
1	Does not respond to mild prodding or shaking

tion of warm. On each study day, sedation score and thermal comfort were obtained three times: (1) before drug administration, (2) before active cooling started, and (3) at the shivering threshold. Volunteers were questioned about side effects during loading dose and infusion period until shivering occurrence. The following side effects were systematically recorded: pain upon study-drug injection, pruritus, bradypnea, dizziness, headache, nausea, vomiting, dry mouth, palpitation, and epigastric pain.

Statistical Analysis

A sustained increase in oxygen consumption (VO_2) exceeding 25% identified the shivering threshold. The baseline for this analysis was the steady-state value (no more than 5% variation in VO_2) after drug infusion but before core cooling started. On each study day, hemodynamic and SpO_2 data were averaged for each volunteer across the cooling period; these values were then averaged for all volunteers. Core and mean skin temperature data, as well as thermal comfort scores (visual analog scale) at the shivering threshold, were averaged across the volunteers for each study day. Sedation levels after drug infusion and at the shivering threshold were presented as the number of subjects having three different modified Observer's Assessment of Alertness/Sedation score (5/4/3; see table 1) on each study day. Results on the four study days for each combination were compared by Kruskal-Wallis test and Student-Newman-Keuls tests for *post hoc* comparison.

The synergistic interactions between nefopam and the two tested drugs (clonidine and alfentanil) were evaluated with the statistical methodology described by Slinker.³⁷ The study was designed as a two-factor experiment with two levels for each factor: the presence and absence of each of the two drugs. Also, assuming an additive effect, the expected reduction for the combination of nefopam and each tested drug was calculated as the sum of the individual effects of nefopam and clonidine or nefopam and alfentanil. With this model, a statistically significant, positive interaction term between the two drugs indicates that they act synergistically or antagonistically. Antagonism in this context simply means that the drug combination produces less effect than would be expected from the sum of the individual effects of each drug. A nonsignificant interac-

Table 2. Nefopam–Clonidine Interaction

	Control	Nefopam	Clonidine	Combination 1
After drug infusion				
Mean arterial pressure, mmHg	91 ± 11	98 ± 14	73 ± 9*†‡	93 ± 8
Heart rate, beats/min	69 ± 9*‡	82 ± 17	61 ± 11*‡	78 ± 12
Spo ₂ , %	99 ± 1	99 ± 1	98 ± 1	99 ± 1
At shivering				
Observer's Assessment of Alertness/Sedation score, 5/4/3	10/0/0	9/1/0	2/8/0†‡	5/5/0†‡
Mean arterial pressure, mmHg	97 ± 11#	106 ± 7#	84 ± 9	100 ± 10*
Heart rate, beats/min	73 ± 12	74 ± 12	59 ± 11†	69 ± 10
Spo ₂ , %	99 ± 1	99 ± 1	99 ± 1	99 ± 1
Total lactated Ringer, /kg	10 ± 4	14 ± 4	17 ± 8†	19 ± 7†
Core cooling rate, °C/h	0.9 ± 0.4	1.4 ± 1.0	1.1 ± 0.7	1.1 ± 0.5
Observer's Assessment of Alertness/Sedation score, 5/4/3	10/0/0	10/0/0	10/0/0	9/1/0
Thermal comfort, VAS	22 ± 8	20 ± 10	17 ± 7	20 ± 13
Mean skin temperature, °C	30.8 ± 0.6	30.2 ± 0.9	30.3 ± 0.6	30.1 ± 0.6
Core temperature, °C	36.5 ± 0.3	35.9 ± 0.3†	36.0 ± 0.3†	35.7 ± 0.2†

* $P < 0.05$ versus Combination 1; † $P < 0.05$ versus Control; ‡ $P < 0.05$ versus Nefopam; # $P < 0.05$ versus clonidine.

Observer's Assessment of Alertness/Sedation = modified Observer's Assessment of Alertness/Sedation Scale; VAS = Visual Analogic Scale.

tion term indicates that the drugs' effects on the shivering threshold are additive.

A repeated-measures ANOVA was used because each volunteer in each drug set received all four treatments. Side effect frequencies were compared using a chi-square test and completed with a Fisher exact test. The software used for statistical tests was StatView version 5.0 (SAS Institute Inc, Cary, IN). Results are expressed as means ± SD; differences and the interaction term were considered statistically significant when $P < 0.05$.

Results

Sixteen volunteers were enrolled in the study for a total of 72 sets of measurements. One volunteer completed only two sets of measurement, and those data were not included in our analysis. Ten volunteers completed four sets of measurement, and five volunteers completed six sets of measurement. For each interaction analysis, data from 10 volunteers were thus available.

Nefopam–Clonidine Interaction

The volunteers were 25 ± 6 yr old, weighed 70 ± 8 kg, and were 179 ± 5 cm tall. Mean loading doses of nefopam and clonidine were 45.5 ± 0.7 mg (0.7 ± 0.1 mg · kg⁻¹) and 170 ± 23 μg, respectively.

After the loading infusion, mean-arterial pressure was significantly lower with clonidine than on the other study days (table 2). Nefopam infusion alone or in combination with clonidine significantly increased heart rate. A significant mild sedation, as defined by the modified Observer's Assessment of Alertness/Sedation, was observed after clonidine alone or in a combination dose compared to control and nefopam study days. Spo₂ values were similar on each study day. All of the volunteers were vasoconstricted before the cold-fluid infusion was started.

At the shivering threshold, mean arterial pressure remained significantly lower with clonidine than on the other study days. Heart rates were also significantly lower with clonidine. Mean skin temperatures at shivering were similar among the four study days. Sedation level at the shivering threshold did not differ among the four study days. Total amount of cold Ringer's Lactate was significantly greater during Clonidine and Combi 1 study days than during Control study day (table 2).

Nefopam reduced the shivering threshold by 0.6 ± 0.3 °C from 36.5 ± 0.3 °C on the control day to 35.9 ± 0.3 °C ($P < 0.001$), and clonidine reduced the shivering threshold by 0.5 ± 0.3 °C to 36.0 ± 0.3 °C ($P < 0.001$). The combination of nefopam and clonidine (Combi1) reduced the shivering threshold by 0.7 ± 0.4 °C to 35.7 ± 0.2 °C ($P < 0.001$). There was a significant interaction between the two drugs in terms of effect on the shivering threshold ($P = 0.034$). The combination of nefopam and clonidine thus reduced the shivering threshold no better than either drug alone, rather than being additive (fig. 1).

Nefopam–Alfentanil Interaction

The volunteers were 25 ± 6 yr old, weighed 70 ± 8 kg, and were 179 ± 5 cm tall. Mean loading doses of nefopam and alfentanil were 45.7 ± 0.6 mg (0.6 ± 0.1 mg · kg⁻¹) and $1,275 \pm 303$ μg (18 ± 5 μg · kg⁻¹), respectively.

After the loading infusion, nefopam infusion alone or in combination significantly increased the heart rate compared to the other study days (table 3). Volunteers were mildly sedated, and Spo₂ was also significantly lower after alfentanil infusion, alone or in combination with nefopam. Mean arterial pressure was similar on each study day. All of the volunteers were vasoconstricted before the cold-fluid infusion was started.

At the shivering threshold, mean-arterial pressure, heart rate, Spo₂ and sedation level did not differ among

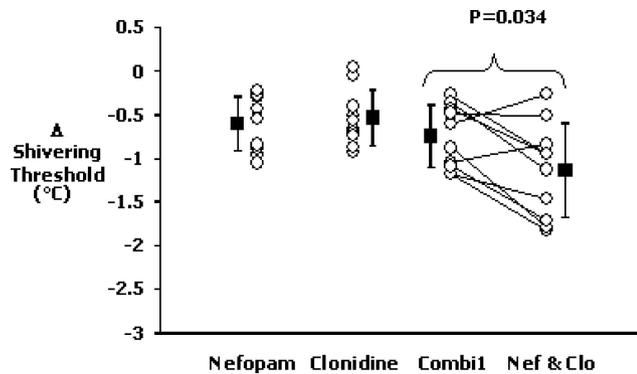


Fig. 1. Reductions in the shivering threshold (compared with the control day) for the Nefopam, Clonidine, and two-drug combination (Combi 1) days. Also shown is the expected reduction for the combination of nefopam and clonidine assuming an additive effect, calculated as the sum of the individual effects of nefopam and clonidine (Nef & Clo). Two-way repeated-measures analysis of variance showed a significant interaction between the effects of the two drugs on the shivering threshold ($P = 0.034$). The relationship was thus significantly nonadditive, with the combination of the two drugs reducing the shivering threshold less than would be expected from their individual effects.

the four study days. Mean skin temperature at shivering was lower during Combination 2 comparatively to Control (respectively $29.9 \pm 0.8^\circ\text{C}$ and $30.8 \pm 0.6^\circ\text{C}$, $P < 0.05$). Thermal comfort was better with the alfentanil infusion than the other days. Significantly more cold Ringer's lactate was required with alfentanil alone, and even more was necessary when alfentanil and nefopam were combined. Core cooling rates were similar among the four study days (table 3).

Nefopam reduced the shivering threshold by 0.7°C from $36.5 \pm 0.3^\circ\text{C}$ on the control day to $35.7 \pm 0.3^\circ\text{C}$ ($P < 0.001$), and alfentanil alone reduced the shivering threshold by 1.0°C to $35.5 \pm 0.7^\circ\text{C}$ ($P < 0.001$). The combination of nefopam and alfentanil (Combination 2) reduced the shivering threshold by $1.8 \pm 0.6^\circ\text{C}$ to $34.5 \pm 0.7^\circ\text{C}$ ($P < 0.001$). There was no interaction between the two drugs in terms of effect on the shiver-

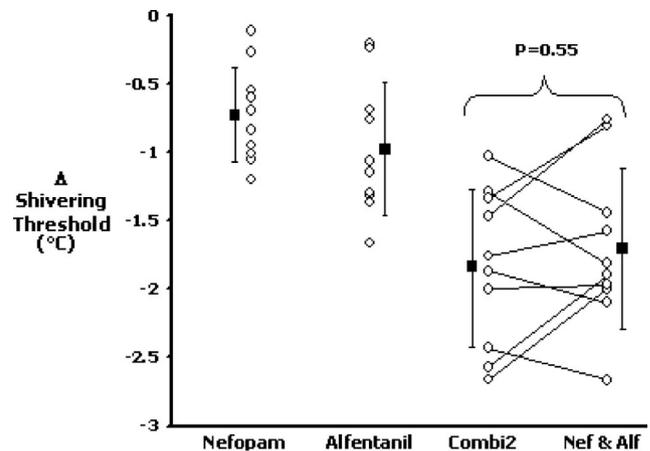


Fig. 2. Reductions in the shivering threshold (compared with the control day) for the Nefopam, Alfentanil, and two-drug combination (Combi 2) days. Also shown is the expected reduction for the combination of nefopam and alfentanil assuming an additive effect, calculated as the sum of the individual effects of nefopam and alfentanil (Nef & Alf). Two-way repeated-measures analysis of variance did not show a significant interaction between the effects of the two drugs on the shivering threshold ($P = 0.55$). The effects were therefore additive, and the combination of the two drugs produced the effect expected based on their individual contributions.

ing threshold ($P = 0.55$). The combination of nefopam and alfentanil was thus *additive* for shivering (fig. 2). A power calculation indicates that there is less than a 10% chance that the interaction is not additive.

Side Effects

Side effects experienced during different interaction studies are summarized in table 4. The volunteers were significantly more likely to become nauseated when nefopam was infused alone or in combination and when alfentanil alone was administered. However, only three volunteers experienced emesis (one during nefopam infusion, one during alfentanil infusion, and one during infusion of nefopam and alfentanil combination). Signif-

Table 3. Nefopam–Alfentanil Interaction

	Control	Nefopam	Alfentanil	Combination 2
After drug infusion				
Mean arterial pressure, mmHg	95 ± 13	102 ± 12	93 ± 14	96 ± 8
Heart rate, beats/minute	70 ± 9	85 ± 16*‡	68 ± 12	89 ± 17*‡
Spo ₂ , %	99 ± 1	99 ± 1	96 ± 4*†	97 ± 2*†
Observer's Assessment of Alertness/Sedation score, 5/4/3	10/0/0	9/1/0	5/5/0*†	5/5/0*†
At Shivering				
Mean arterial pressure, mmHg	97 ± 11	103 ± 10	93 ± 14	99 ± 7
Heart rate, bpm	66 ± 13	76 ± 17	68 ± 13	72 ± 9
Spo ₂ , %	99 ± 1	99 ± 1	98 ± 2	99 ± 1
Total lactated Ringer's, /kg	9 ± 4	18 ± 7	28 ± 13*	53 ± 14*‡†
Core cooling rate, °C/h	0.9 ± 0.5	1.5 ± 0.9	1.5 ± 0.5	1.2 ± 0.4
Observer's Assessment of Alertness/Sedation score, 5/4/3	10/0/0	10/0/0	6/3/1*†	7/3/0
Thermal comfort, VAS	27 ± 6	24 ± 12	37 ± 11*†	41 ± 12*†
Mean skin temperature, °C	30.8 ± 0.6	30.3 ± 0.6	30.5 ± 0.6	29.9 ± 0.8*
Core temperature, °C	36.5 ± 0.3	35.7 ± 0.3*	35.5 ± 0.7*	34.5 ± 0.7*‡†

* $P < 0.05$ versus Control; † $P < 0.05$ versus Nefopam; ‡ $P < 0.05$ versus Alfentanil.

Observer's Assessment of Alertness/Sedation score = modified Observer's Assessment of Alertness/Sedation Scale; VAS = Visual Analogic Scale.

Table 4. Side Effects

	Control	Nefopam	Clonidine	Combination 1	Alfentanil	Combination 2
Nausea	0%	80%*†	10%	50%*	40%*	50%*
Vomiting	0%	7%	0%	0%	10%	10%
Pain at injection	0%	60%*†‡	10%	70%*†‡	0%	20%
Sweating	0%	13%	0%	10%	0%	30%
Dry mouth	0%	13%	10%	20%	30%*	80%*
Pruritus	0%	7%	10%	0%	70%* †§	50%* §
Bradypnea	0%	0%	0%	0%	30%	10%
Dizziness	0%	13%	0%	20%	10%	30%

* $P < 0.05$ versus Control; † $P < 0.05$ versus Clonidine; ‡ $P < 0.05$ versus Alfentanil; § $P < 0.05$ versus Combination 1; || $P < 0.05$ versus Nefopam.

icantly more volunteers complained about having pain upon loading-dose injection when nefopam was infused alone or in combination with clonidine than other study days. Significantly more volunteers complained about having a dry mouth during the study when alfentanil was infused alone compared to Control or when it was combined with nefopam compared to all the other studied drugs. Pruritus occurred more frequently when alfentanil was infused alone or in combination with nefopam compared to all the other studied drugs. Also, bradypnea was observed more frequently when alfentanil was infused alone. There were six episodes of profuse sweating during the initial 30 min of nefopam administration.

All side effects spontaneously resolved within a few minutes after completion of the loading infusions, with the exception of a single volunteer, who experienced a second episode of vomiting during the maintenance of alfentanil infusion.

Discussion

Our results confirm that nefopam reduces the shivering threshold without substantial toxicity. And combining nefopam with a small dose of alfentanil additively reduced the shivering threshold; that is, the combination reduced the shivering threshold as much as would be expected from the sum of the individual effects of each drug. These data thus support supplementing nefopam with an opioid if the nefopam alone is insufficient to block shivering. In contrast, combining nefopam with clonidine was ineffective and did not further reduce the shivering threshold. This combination thus appears to offer no advantage in terms of inducing therapeutic hypothermia.

There is currently little basis for recommending a specific target temperature for therapeutic hypothermia. Nonetheless, target temperatures from 33°C to 34°C are being used clinically by some physicians and in ongoing clinical trials.^{7,8,38} The combination of nefopam and alfentanil reduced the shivering threshold to 34.5°C, which some might consider insufficiently hypothermic. However, the observed shivering threshold of 34.5°C must be interpreted in light of physiology of thermoreg-

ulatory shivering. We set mean skin temperature to 30–31°C, which is 3 to 4°C less than typical for stroke patients in a ward or intensive care unit setting. We used this low skin temperature with the aim of raising the shivering threshold and minimizing the risk from infusion of large amounts of cold fluid. Because skin temperature contributes 20% to control of shivering,³⁹ each degree centigrade of cutaneous warming will compensate for approximately 0.2°C core hypothermia; the threshold at a more typical skin temperature would thus have been well under 34°C. An additional factor to consider is that most stroke victims are elderly. Advanced age *per se* impairs thermoregulatory responses.^{40,41} It should thus be possible to induce comparable hypothermia in the elderly with even smaller drug doses or to induce greater hypothermia with similar drug doses.

The vasoconstriction threshold is of considerable interest, because vasoconstriction is an effective thermoregulatory response. Vasoconstriction is the primary autonomic defense against cool environments; once triggered, it prevents further hypothermia, even in anesthetized patients.³⁶ It is thus difficult to reduce the core temperature below the vasoconstriction threshold with surface cooling. Internal cooling, such as we used, has no such limitation because heat is removed directly from the core thermal compartment. A further advantage of internal cooling is that it can be combined with simultaneous gentle cutaneous warming, which improves thermal comfort⁴² and reduces the vasoconstriction and shivering thresholds.⁴³

Nearly all antishivering drugs comparably reduce the vasoconstriction and shivering thresholds. An exception is meperidine, which disproportionately reduces the shivering threshold.⁴⁴ In contrast, the vasoconstriction threshold is unchanged with nefopam.²¹ That vasoconstriction and shivering can be modulated independently is clinically important. Thermoregulatory vasoconstriction restrains heat content in the core compartment, and it thus speeds and prolongs core temperature changes when heat is directly removed from the thermal core.

Different combinations of antishivering drugs have been evaluated. In all cases, meperidine was tested in

combination with other drugs, including buspirone,¹⁸ dexmedetomidine,¹⁷ or magnesium,⁴⁵ because of its special antishivering effect.⁴⁴ The combination of meperidine and the anxiolytic-drug buspirone has a favorable synergistic interaction.¹⁸ For example, a combination of $0.3 \mu\text{g} \cdot \text{ml}^{-1}$ intravenous meperidine and 30 mg of oral buspirone reduced the shivering threshold by 2.3°C at a mean skin temperature near 32°C . In the current study, we found that the combination of nefopam ($100 \text{ ng} \cdot \text{ml}^{-1}$) and alfentanil ($150 \text{ ng} \cdot \text{ml}^{-1}$) reduces shivering threshold by 2.0°C , which is similar. Thus, association of nefopam and a μ -agonist represents an interesting option for avoiding thermoregulatory shivering when therapeutic hypothermia is induced.

Numerous sites are involved in the control of the thermoregulatory shivering. Supraspinal sites are located in the hypothalamus, the pons, and the mesencephalon.²⁴ Nefopam is a strong inhibitor of serotonin in the corpus striatum and of norepinephrine in the hypothalamus.⁴⁶ and also has an effect in the pons. Clonidine activates presynaptic α_2 -adrenoceptors, which are present in sympathetic nerve endings and noradrenergic neurons in the central nervous system.⁴⁷ The locus coeruleus located in the upper brainstem is the largest noradrenergic cell group in the brain,⁴⁷ and the locus subcoeruleus, which is a circumscribed area ventromedially to the locus coeruleus, appears to be one of the most important relay station in the transmission of thermal information.²⁴

Clonidine and nefopam presumably both impair shivering *via* the monoamine pathway and could do so at many levels of the neuraxis. However, a combination of the two drugs was significantly less effective than might be expected from their individual actions. The fact that the threshold with the two drugs combined was similar to the lower threshold with the separate thresholds, suggests the existence of a ceiling effect when both drugs are administered simultaneously. Adding a second drug in this context thus increases toxicity without (much) improving the desired therapeutic effect on shivering.

Nefopam directly interacts with α_1 - and α_2 -adrenoceptors,²² as well as antagonizing *N*-Methyl-D-Aspartate receptors.²³ Nefopam is not an opiate and does not interact with opiate receptors.⁴⁸ Alfentanil is a pure μ receptor agonist, and μ receptors are known to participate in central thermoregulatory control.²⁴ Additive effects of nefopam and alfentanil suggest that different pathways participate. Adding a second drug in this context is thus beneficial in that it improves the therapeutic effects and does so with minimal total toxicity.

A limitation of our study is that we did not measure blood concentrations of nefopam at shivering. However, the pharmacokinetic model we used is identical to that used in our previous study where blood was sampled at the sweating, vasoconstriction, and shivering thresholds. Target concentrations were $35 \text{ ng} \cdot \text{ml}^{-1}$ and $70 \text{ ng} \cdot \text{ml}^{-1}$. At

the first thermoregulatory threshold (sweating), plasma concentrations were respectively 32 ± 6 and $70 \pm 16 \text{ ng} \cdot \text{ml}^{-1}$. On each study day, the plasma concentrations decreased with time; but the concentrations at the shivering thresholds (respectively, 28 ± 4 and $55 \pm 11 \text{ ng} \cdot \text{ml}^{-1}$) were not significantly lower than at the sweating threshold. On the basis of our previous experience, we thus assume that plasma concentrations were close to target values and, more importantly, similar on each study day under the circumstances of the current study.

Based on previous experience with nefopam,^{49,50} the side effects reported by our volunteers were expected. As in previous studies,²¹ adverse events resolved spontaneously within 30 min even though the nefopam infusion continued. This pattern suggests that the toxicity is associated with rapid increases in cerebral concentration during loading, rather than steady-state concentrations *per se*. Bradypnea was observed in three volunteers during alfentanil infusion alone and in one volunteer when nefopam was combined with alfentanil. However, no profound decreases in oxygen saturation were observed, and concomitant administration of oxygen was never necessary. Alfentanil produced light sedation in some volunteers, but they remained responsive throughout.

Our nefopam loading dose of approximately 45 mg was about twice that usually prescribed for postoperative analgesia. Although there is not enormous experience with such a high dose, it appears to be safe.²⁶ For example, fatal overdose with nefopam has been reported only three times since the beginning of 1980s. In every case, blood concentration was 30–100 times the highest therapeutic concentrations.³¹ New Zealand⁵⁰ and French⁴⁹ studies reviewed adverse drug reactions associated with nefopam over 10- to 12-yr periods. Only few toxicities were reported, and most of them were expected (nausea, sweating, dizziness, tachycardia, and vomiting). Among those considered as serious, most were neuropsychiatric (confusion, hallucination, delirium, or convulsion), cardiovascular (arterial hypotension, heart failure), or cutaneous or anaphylactic disorders and occurred at therapeutic dosage. All but one resolved after nefopam withdrawal.

In summary, nefopam and alfentanil additively reduced the shivering threshold in healthy adults. The doses we tested decreased the threshold by approximately 2°C , with only minimal respiratory toxicity. This combination might thus facilitate studies evaluating the putative benefits of therapeutic hypothermia.

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