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## Clonidine and Ketanserin Both Are Effective Treatment for Postanesthetic Shivering

Jean Joris, M.D.,\* Maryse Banache, M.D.,† Francis Bonnet, M.D.,‡ Daniel I. Sessler, M.D.,§ Maurice Lamy, M.D.¶

**Background:** Although meperidine is an effective treatment of postanesthetic shivering, its mechanism of action remains unknown. Investigation of other drugs might help clarify the mechanisms by which shivering can be controlled. Accordingly, we investigated the efficacy of clonidine, an  $\alpha_2$ -adrenergic agonist, and ketanserin, a 5-hydroxytryptamine antagonist, in treating postanesthetic shivering.

**Methods:** First, 54 patients shivering after general anesthesia were allocated randomly to receive an intravenous bolus of saline, 150  $\mu$ g clonidine, or 10 mg ketanserin. A second study explored the dose-dependence of clonidine. Forty shivering patients were given saline or clonidine, 37.5, 75, or 150  $\mu$ g.

**Results:** The duration of shivering was significantly shorter in those given clonidine ( $2.1 \pm 0.9$  min) than in the other two groups and shorter in the ketanserin group ( $4.3 \pm 0.9$  min) than in the saline group ( $12.0 \pm 1.6$  min). Clonidine and ketanserin significantly decreased systolic arterial blood pressure when compared to saline. Core rewarming was significantly slower in the clonidine group. In the second study, 37.5  $\mu$ g clonidine was no more effective than saline. Two minutes after treatment, 150  $\mu$ g obliterated shivering in all patients. Five minutes after treatment, all patients given 75  $\mu$ g had

stopped shivering. Systolic arterial pressure and heart rate decreased significantly in patients given 75 and 150  $\mu$ g clonidine.

**Conclusions:** Clonidine (150  $\mu$ g) and ketanserin (10 mg) both are effective treatment for postanesthetic shivering. The effect of clonidine on shivering is dose-dependent: whereas 37.5  $\mu$ g had no effect, 75  $\mu$ g clonidine stopped shivering within 5 min. (Key words: Anesthetic complications: shivering. Sympathetic nervous system,  $\alpha_2$ -adrenergic agonist: clonidine. Sympathetic nervous system, 5-HT<sub>2</sub> antagonist: ketanserin. Temperature: hypothermia; shivering; thermoregulation.)

SHIVERING is common during recovery from general anesthesia. Besides being unpleasant, the increase in oxygen consumption may produce complications in patients with coronary artery disease or cardiac failure. Optimal pharmacologic treatment of shivering requires an effective drug with few side effects. Meperidine reportedly is more effective than the other opioids in stopping postoperative shivering,<sup>1,2</sup> but the mechanism(s) by which it stops shivering remains virtually unknown. Although 25 mg meperidine rarely causes complications, it may interact synergistically with previously administered opioids or anesthetics to cause respiratory depression or prolong the requirement for ventilatory support. Investigating other drugs may help clarify the biochemical pathways of shivering thermogenesis and the mechanisms by which shivering can be pharmacologically controlled.

Clonidine, an  $\alpha_2$ -adrenergic receptor agonist, and ketanserin, a 5-hydroxytryptamine (5-HT<sub>2</sub>) receptor antagonist, each reportedly reduce postanesthetic shivering.<sup>3-#</sup> Furthermore, clonidine apparently prevents postanesthetic shivering when administered before or during surgery.<sup>4-6</sup> Nevertheless, data concerning the effect of these drugs on shivering are sparse and controversial. Indeed, a recent study failed to confirm the efficacy of clonidine for treatment of postanesthetic shivering.<sup>7</sup> Additionally, both clonidine and ketanserin can induce undesirable hemodynamic changes, such as hypotension. Accordingly, we compared the effects

\* Assistant Professor, Department of Anesthesiology, University Hospital of Liège, Belgium.

† Resident, Department of Anesthesiology, University Hospital of Liège, Belgium.

‡ Professor, Department of Anesthesiology, Hôpital Henri Mondor, Créteil, France.

§ Associate Professor of Anesthesia, Department of Anesthesia, University of California, San Francisco, California.

¶ Professor and Chairman, Department of Anesthesiology, University Hospital of Liège, Belgium.

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Address reprint requests to Dr. Joris: Department of Anesthesiology, CHU of Liège, Domaine du Sart Tilman, B-4000 Liège, Belgium.

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## CLONIDINE AND KETANSERIN FOR SHIVERING

of clonidine and ketanserin on shivering and evaluated the dose-dependence of clonidine.

## Patients and Methods

Two studies were conducted after approval of our institution's Ethics Committee and consent of the involved patients. Patients in each study were scheduled for abdominal, orthopedic, or urologic surgery. Patients with respiratory or cardiac failure were excluded from the study, as were patients previously given clonidine or other  $\alpha_2$  agonists. General anesthesia was induced with thiopental (5 mg/kg) or propofol (2 mg/kg) and sufentanil (10–15  $\mu$ g). Atracurium (0.5 mg/kg) was administered to facilitate orotracheal intubation, and anesthesia was maintained with 50% N<sub>2</sub>O in oxygen and isoflurane, enflurane, halothane, or propofol. After surgery, patients were transferred to the postanesthesia care unit.

Sixty ASA physical status 1 and 2 adult patients were included in the first study. Upon arrival in the postanesthesia care unit, shivering patients were assigned randomly to receive one of the three following treatments: intravenous bolus injection of isotonic saline, 150  $\mu$ g clonidine, or 10 mg ketanserin. Only intense shivering, presenting as tremor of the head, jaw, and arms and associated with piloerection, was included in the study to avoid spontaneous disappearance of shivering during setup and connection of the monitors and baseline measurements. The effect of treatment on shivering was assessed by the anesthesiologist in charge of the postanesthesia care unit, who was not aware of the administered drug. Time elapsed between the intravenous bolus injection and the complete disappearance of shivering was defined as the duration of shivering. Oscillometric arterial blood pressure, heart rate (Cardiacap, Datex, Helsinki, Finland), and rectal temperature (78354 A Hewlett Packard, Bolingen, Germany) were recorded before and 1, 5, 10, 15, 30, 60, and 120 min after the bolus injection.

In the second study, inclusion criteria were identical, and the conditions of surgery and general anesthesia comparable. Forty patients shivering after surgery were allocated randomly to one of four groups ( $n = 10$  in each group): intravenous saline (no clonidine) or 37.5, 75, or 150  $\mu$ g clonidine. The effect on shivering of each intravenous bolus was assessed by an observer blinded to patient allocation, 2 and 5 min after treatment, according to the following scale: 0 = no effect,

1 = partial inhibition, and 2 = total inhibition. Oscillometric arterial blood pressure, heart rate, and rectal temperature were recorded before and 5 and 60 min after the bolus injection.

Time-dependent values were compared using the method of Zerbe.<sup>8</sup> This technique allows one to test the hypothesis of the equality of response curves for two or more groups at multiple time points or during any time interval. Its criterion is distributed as a Snedecor F test whose degrees of freedom depend not only on the group sample sizes but also on the time period chosen. Two-tailed, unpaired Student's *t* test was used when appropriate. Log-rank test was used to compare the evolution of percentage of patients shivering in the three groups at each time. Results are reported as mean  $\pm$  SD;  $P < 0.05$  was considered statistically significant.

## Results

### Study 1

Six patients were excluded retrospectively. In three cases, positive blood cultures (resulting from urologic endoscopic procedures) suggested that shivering was related to sepsis. Incorrect group assignment or protocol deviation accounted for the exclusion of the other three. The 54 remaining patients were distributed among the three groups that were comparable with regard to morphometric characteristics and anesthetic techniques (table 1).

Survival curves for shivering, representing the number of patients shivering as a function of time, differed significantly in the three groups. Patients given clonidine and ketanserin had a significantly shorter duration of shivering than those given saline ( $P < 0.01$ ): clonidine =  $2.1 \pm 0.9$  min, ketanserin =  $4.3 \pm 0.9$  min, and saline =  $12.0 \pm 1.6$  min (median values: saline 12

**Table 1. Demographics and Anesthetic Agents in the Three Groups of Study 1**

	Isotonic Saline	Clonidine	Ketanserin
Age (yr) (mean $\pm$ SD)	41 $\pm$ 16	36 $\pm$ 15	34 $\pm$ 9
Gender: M/F	12/7	12/3	15/5
Isoflurane	5	3	7
Enflurane	11	11	11
Halothane	3	0	1
Propofol	0	1	1

min, ketanserin 2 min, and clonidine 1 min). Although clonidine acted significantly faster than ketanserin ( $P < 0.05$ ), clonidine and ketanserin were equally effective 10 min after the bolus injection. At that time, the percentage of patients still shivering was 58%, 5%, and 7%, respectively, in the saline, ketanserin, and clonidine groups ( $P < 0.05$ ; fig. 1).

Before treatment, mean core temperature was similar in the three groups: saline  $35.6 \pm 0.8^\circ\text{C}$ , clonidine  $35.5 \pm 0.6^\circ\text{C}$ , and ketanserin  $35.6 \pm 0.8^\circ\text{C}$ . Rewarming, however, appeared somewhat slower in the clonidine group than in the patients given saline ( $P = 0.056$ ), and body temperature was significantly lower in the clonidine group 30–120 min after treatment. The rate of core rewarming was similar among patients given saline and those given ketanserin (fig. 2).

Systolic arterial pressure and heart rate decreased significantly in each group (table 2), but the reductions in systolic arterial pressure and heart rate were greater in the patients given clonidine than in those given saline ( $P < 0.05$  and  $P = 0.07$ , respectively). Systolic arterial pressure decreased to less than 100 mmHg in only two patients given clonidine and one given ketanserin. Mean arterial pressure remained above 60 mmHg in all patients, and none required treatment for hypotension. Two patients given clonidine had heart rates between 45 and 50 beats/min, but for only one or two consecutive measurements. One patient given ketanserin maintained a heart rate near 48 beats/min from the 30-min measurement until the study concluded.

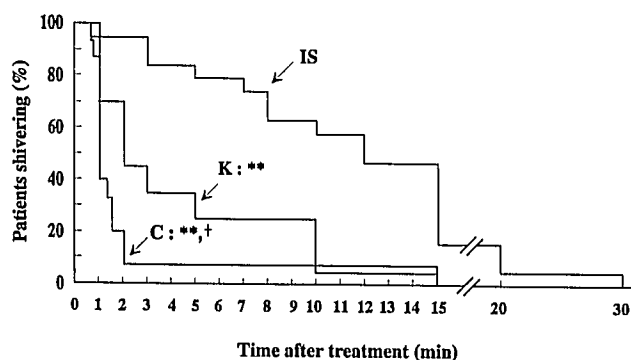


Fig. 1. Duration of shivering expressed as survival curves. Patients received an intravenous bolus of isotonic saline (IS), 10 mg ketanserin (K), or  $150\text{ }\mu\text{g}$  clonidine (C). \*\* $P < 0.01$  was considered a significant difference versus saline. † $P < 0.05$  was considered a significant difference versus ketanserin.

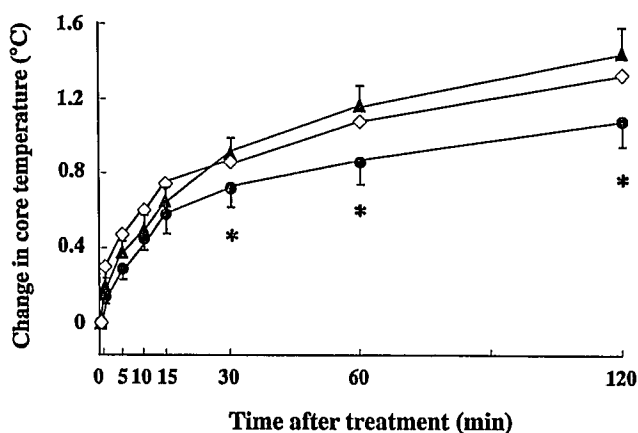


Fig. 2. Change in core temperature (mean  $\pm$  SEM) in shivering patients treated by an intravenous bolus of isotonic saline ( $\blacktriangle$ ), 10 mg ketanserin ( $\diamond$ ), or  $150\text{ }\mu\text{g}$  clonidine ( $\bullet$ ). SEMs of the K group were omitted for clarity (SEMs ranged from  $0.05^\circ$  to  $0.12^\circ\text{C}$  and were similar to SEMs of the two other groups). \* $P < 0.05$  was considered a significant difference versus saline.

### Study 2

Morphometric characteristics and anesthetic techniques were similar in the four groups (table 3).

The effect of clonidine on shivering was dose-dependent. The  $150\text{-}\mu\text{g}$  dose of clonidine stopped shivering in all the patients within 2 min. Two minutes after injection of  $75\text{ }\mu\text{g}$  clonidine, shivering was abolished in seven patients and reduced in the three others. Within 5 min after treatment, all patients in this group stopped shivering. In contrast,  $37.5\text{ }\mu\text{g}$  clonidine had no significant effect when compared to saline.

The decrease in mean arterial pressure was significantly greater after the administration of 75 and  $150\text{ }\mu\text{g}$  clonidine than after saline or  $37.5\text{ }\mu\text{g}$  clonidine, but no significant differences were detected between the 75 and  $150\text{ }\mu\text{g}$  groups. Heart rate did not differ significantly among the groups (fig. 3).

### Discussion

Our data confirm that both  $150\text{ }\mu\text{g}$  clonidine and 10 mg ketanserin are effective treatments for postoperative shivering. This dose of clonidine, however, acted slightly more rapidly than 10 mg ketanserin. Our second study indicates that the effect of clonidine is dose-dependent and that  $75\text{ }\mu\text{g}$  clonidine administered as an intravenous bolus is sufficient to treat postanesthetic shivering.

## CLONIDINE AND KETANSERIN FOR SHIVERING

Table 2. Effect of Isotonic Saline, 10 mg Ketanserin, and 150  $\mu$ g Clonidine on Heart Rate and Arterial Pressure

	0	1 min	5 min	10 min	15 min	30 min	60 min	120 min
HR (beats/min)								
IS	86 $\pm$ 22	82 $\pm$ 21	76 $\pm$ 17*	74 $\pm$ 18*	75 $\pm$ 19*	74 $\pm$ 16*	75 $\pm$ 20*	79 $\pm$ 16*
K	83 $\pm$ 10	83 $\pm$ 15	74 $\pm$ 13*	73 $\pm$ 14*	70 $\pm$ 11*	68 $\pm$ 12*	68 $\pm$ 13*	70 $\pm$ 14*
C	83 $\pm$ 19	70 $\pm$ 13*	69 $\pm$ 15*	66 $\pm$ 14*	63 $\pm$ 12*	64 $\pm$ 12*	64 $\pm$ 13*	71 $\pm$ 15*
SAP (mmHg)								
IS	142 $\pm$ 19	143 $\pm$ 17	138 $\pm$ 22	139 $\pm$ 22	138 $\pm$ 18	133 $\pm$ 19*	128 $\pm$ 13*	125 $\pm$ 15*
K	141 $\pm$ 23	129 $\pm$ 19*	124 $\pm$ 18*	124 $\pm$ 19*	125 $\pm$ 17*	124 $\pm$ 10*	122 $\pm$ 16*	124 $\pm$ 16*
C	139 $\pm$ 25	135 $\pm$ 30	122 $\pm$ 21*	119 $\pm$ 20*	122 $\pm$ 22*	119 $\pm$ 20*	117 $\pm$ 20*	115 $\pm$ 20*
DAP (mmHg)								
IS	77 $\pm$ 12	74 $\pm$ 10	72 $\pm$ 8	74 $\pm$ 12	74 $\pm$ 9	72 $\pm$ 11	73 $\pm$ 10	72 $\pm$ 8
K	86 $\pm$ 27	73 $\pm$ 18*	73 $\pm$ 16*	75 $\pm$ 16*	72 $\pm$ 12*	71 $\pm$ 12*	72 $\pm$ 12*	69 $\pm$ 12*
C	79 $\pm$ 19	83 $\pm$ 37	69 $\pm$ 16	65 $\pm$ 17*	70 $\pm$ 18*	70 $\pm$ 18*	68 $\pm$ 18*	65 $\pm$ 15*

Data are mean  $\pm$  SD.

HR = heart rate; SAP = systolic arterial pressure; DAP = diastolic arterial pressure.

HR, SAP, and DAP were recorded before (0), 1, 5, 10, 15, 30, 60, and 120 min after an IV bolus injection of isotonic saline (IS), 10 mg ketanserin (K), or 150  $\mu$ g clonidine (C).

\* Difference is statistically significant ( $P < 0.05$ ) compared with time 0. For HR, comparison C versus IS ( $P < 0.05$  at time 15, 30 min); for SAP, comparison C versus IS ( $P < 0.05$  from 5 to 120 min), K versus IS ( $P < 0.05$  from 1 to 15 min).

Nalda *et al.*<sup>3</sup> have shown that 5 min after injection, 10 mg ketanserin decreased shivering in ASA physical status 1 patients recovering from gynecologic surgery. Shivering in hypothermic patients recovering from general anesthesia is preceded by peripheral vasoconstriction, leading to decreased skin temperature.<sup>3</sup> Subsequent stimulation of cutaneous cold receptors contributes to maintenance of shivering. Nalda *et al.* hypothesized that vasodilation induced by ketanserin<sup>3,9</sup> increases skin temperature<sup>3</sup> and may alter this peripheral component of shivering. A central mechanism, however, also remains likely. Larger doses of ketanserin probably would act more rapidly but also might produce more arterial hypotension.

Two recent studies using an infusion of 5  $\mu$ g/kg clonidine over 1 h<sup>7</sup> or over 3 h<sup>10</sup> failed to demonstrate any therapeutic or preventive effect of clonidine on postoperative shivering. Since shivering occurs early in the postoperative period and usually stops spontaneously within 30 min, prolonged infusions of clonidine would not seem optimal because peak plasma concentrations of clonidine will not be reached until after shivering disappears spontaneously. Furthermore, these infusion regimens presumably resulted in relatively low plasma concentration of clonidine compared to the peak concentrations obtained after an intravenous bolus injection of 150, or even 75,  $\mu$ g clonidine. However, the initial report showed that an intravenous bolus

of 150  $\mu$ g clonidine dramatically reduced or abolished shivering.<sup>#</sup> Prevention of postoperative shivering by clonidine given before or during anesthesia also has been proposed.<sup>4,5</sup> Finally, clonidine, administered over a short period at the end of surgery and before the onset of shivering, blunted the increase in oxygen consumption associated with shivering during the early phase of recovery.<sup>6</sup> Consistent with these data, we report a distinct and rapid effect of clonidine on shivering.

Clonidine has central and peripheral effects, both of which may account for its antishivering action. Clonidine induces cutaneous vasoconstriction secondary to the stimulation of peripheral  $\alpha_2$  and  $\alpha_1$  adrenoreceptors.<sup>11,12</sup> However, vasoconstriction would reduce skin temperature, stimulate cutaneous cold thermo-

Table 3. Demographics and Anesthetic Agents in the Four Groups of Study 2

	Dose of Clonidine ( $\mu$ g)			
	0	37.5	75	150
Age (yr) (mean $\pm$ SD)	31 $\pm$ 15	38 $\pm$ 15	38 $\pm$ 15	43 $\pm$ 15
Gender: M/F	8/2	4/6	9/1	8/2
Enflurane	6	7	7	2
Halothane	1	1	1	3
Isoflurane	3	2	2	5

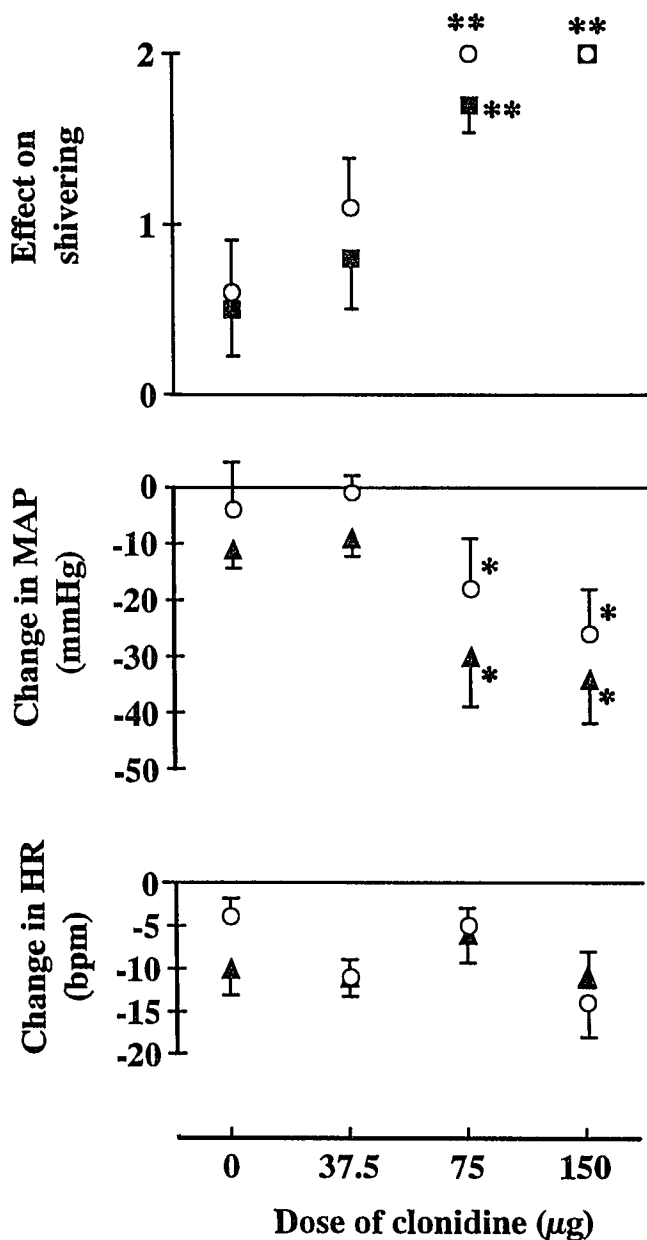


Fig. 3. Dose-response of clonidine on shivering, mean arterial pressure (MAP), and heart rate (HR). Patients were treated with 0, 37.5, 75, or 150 µg clonidine. Effect on shivering was assessed 2 (■) and 5 (○) min after treatment: 0 = no effect, 1 = partial inhibition, 2 = total inhibition. Changes in MAP (mmHg) and HR in beats/min were recorded 5 (○) and 60 (▲) min after treatment. Data are mean  $\pm$  SEM. \* $P < 0.05$  was considered a significant change versus 0 and 37.5 µg clonidine. \*\* $P < 0.01$  = was considered a significant change versus 0 and 37.5 µg clonidine.

receptors, and consequently, aggravate shivering. Peripheral mechanisms, therefore, seem unlikely to contribute substantially to the effect of clonidine on shivering. Conversely, clonidine may inhibit transmission of afferent thermal signals at the level of the spinal cord, decrease the central thermoregulatory threshold for shivering, or depress the efferent pathways responsible for shivering. The rapid diminution in shivering intensity after the administration of clonidine and the nature of this response (almost all or none) suggest a resetting of the central threshold for shivering. Supporting this hypothesis is the observation that central administration of norepinephrine decreases core temperature.<sup>13</sup> Finally, the density of  $\alpha_2$ -adrenergic receptors is high in the hypothalamus.<sup>14</sup> Further studies are required to confirm a centrally mediated effect of clonidine on shivering.

In the dose-range studied, clonidine treatment stopped postanesthetic shivering more rapidly than did ketanserin. The differences, however, were small and might only reflect kinetic or dose-dependent effects. For example, the 75-µg dose of clonidine may have a time course similar to that of 10 mg ketanserin. A dose-response evaluation of ketanserin would address these issues.

Our investigations focused more on clonidine than on ketanserin because there are more experimental thermoregulatory data involving  $\alpha$  adrenoreceptors than serotonergic receptors.<sup>4-6,13-17,18</sup> Furthermore, it is likely that new, highly specific  $\alpha_2$ -agonist agents, such as dexmedetomidine<sup>17</sup> and mivazerol,<sup>18</sup> soon will be available clinically.

Patients respond to core hypothermia with vasoconstriction and shivering thermogenesis.<sup>19</sup> The significantly slower rewarming observed after cessation of shivering by clonidine confirms the efficacy of shivering as a thermoregulatory response. Similarly, central administration of norepinephrine decreases thermogenesis and increases cutaneous blood flow, causing hypothermia.<sup>13</sup> In contrast, whereas ketanserin also rapidly stopped postoperative shivering, it did not significantly impair patient rewarming. These observations suggest that vasoconstriction constrained metabolic heat to the core more in patients given ketanserin than in those given clonidine. The difference in core temperature observed 2 h after administration of clonidine or ketanserin is only 0.3°C and probably is not clinically relevant. Nonetheless, because rewarming may be slower after effective treatment of shivering,

## CLONIDINE AND KETANSERIN FOR SHIVERING

these patients may require active treatment of hypothermia to prevent its continuing side effects, including prolonged duration of drug action,<sup>20</sup> impaired coagulation,<sup>21</sup> negative nitrogen balance,<sup>22</sup> and possibly, risk of infection.<sup>23</sup> Consequently, maintaining perioperative normothermia is preferable to postoperative treatment of shivering.

Shivering is associated with vasoconstriction as well as increases in heart rate and arterial blood pressure.<sup>24</sup> Not surprisingly, treatment of shivering reverses these hemodynamic changes. However, clonidine *per se* contributes to this reversal; systolic arterial blood pressure and heart rate were significantly lower in patients treated with clonidine than in those given saline, even after cessation of shivering. The hemodynamic consequences of effective doses of clonidine and ketanserin are beneficial for shivering patients, rather than deleterious. Indeed, these treatments returned elevated arterial blood pressure and heart rate to the normal range. It is likely that the decrease in blood pressure will be more pronounced, and perhaps deleterious, when clonidine is administered to hypovolemic patients.

Both clonidine and ketanserin have terminal half-lives exceeding 10 h.<sup>25-26</sup> After the rapid distribution phase following intravenous injections, their plasma concentrations remain relatively high and nearly constant for a longer period than required for these studies.<sup>25-27</sup>

Our study does not allow us to determine what constitutes the best treatment for postanesthetic shivering. Meperidine is considered to be the drug of choice for the treatment of shivering in spontaneously breathing patients.<sup>24,28</sup> Inclusion of a meperidine group as a positive control and a dose-response study with ketanserin, therefore, would have been appropriate to compare the different pharmacologic agents. Intravenous administration of 25–50 mg meperidine reduces or abolishes postoperative shivering in 50–60% of patients.<sup>24,28</sup> In our study, the percentage of patients still shivering was 79%, 25%, and 7%, respectively, in the saline, ketanserin, and clonidine groups. The duration of a single dose of meperidine may be relatively short, necessitating repeated doses. Because ketanserin and clonidine have long half-lives, repeated doses are not required. Though both these drugs decrease arterial blood pressure, hypotension also may occur in hypo-

volemic patients given meperidine. The risk of respiratory depression after small doses of meperidine, although small, is increased when repeated doses are given.

Clonidine contributes to pain relief without potentiating opioid-induced respiratory depression.<sup>29</sup> The sedative effect of clonidine is not necessarily undesirable in the immediate postoperative period, particularly after invasive surgical procedures producing discomfort. Finally, in addition to all these pharmacologic treatments associated with potential side effects, skin-surface warming also is effective in treating postanesthetic shivering<sup>\*\*</sup> without inducing undesirable effects.

In the second study, therefore, we asked whether smaller doses of clonidine also might be effective, but perhaps have fewer hemodynamic effects. The 75- $\mu$ g bolus was almost as effective as the 150- $\mu$ g bolus; both doses, however, produced similar hemodynamic changes. The hemodynamic effects of clonidine are complex, resulting from peripheral vasoconstriction combined with the inhibition of the sympathetic activity mediated by stimulation of spinal and supraspinal  $\alpha_2$  and/or imidazoline receptors.<sup>30-32</sup> Moreover, plasma concentrations of clonidine are not linearly related to the dose of clonidine,<sup>25</sup> and biphasic responses of arterial blood pressure have been observed also.<sup>33</sup> Furthermore, transient hypertension due to stimulation of vascular  $\alpha_2$ -adrenergic receptors has been reported when an intravenous bolus of clonidine is administered.<sup>34</sup> However, we, and others,<sup>35,36</sup> did not observe arterial hypertension. The multiple, and sometimes conflicting, mechanisms of action of clonidine on blood pressure may explain the absence of a significant hemodynamic difference between patients given 75 and 150  $\mu$ g clonidine. Since shivering *per se* causes hypertension and tachycardia, inclusion of shivering at different intensities might have obscured hemodynamic differences between patients given 75 and 150  $\mu$ g clonidine.

Although quantification of shivering by oxygen consumption would have been ideal, only intense shivering was included in our studies, and baseline hemodynamic parameters did not differ significantly among the four groups. Despite similar hemodynamic changes, the lower dose of clonidine is likely to produce fewer side effects<sup>25</sup> and, therefore, would be preferred in most cases.

Patients in this study were given a variety of volatile anesthetics and opioid adjuvants. Had within-group

<sup>\*\*</sup> Mort T, Rintel T, Altman F: Shivering in the cardiac patient: Evaluation of the Bair Hugger warming system (abstract). *ANESTHESIOLOGY* 73:A239, 1990.

variability been high, this would be a serious weakness of the study because we did not have sufficient patients to analyze each anesthetic type separately. However, responses within each treatment group were remarkably homogenous. Our data thus indicate that both clonidine and ketanserin are rapid and effective treatments in patients given a wide variety of anesthetics.

In conclusion, 150 µg clonidine and 10 mg ketanserin each stopped postoperative shivering without producing clinically important side effects. However, clonidine acted slightly more rapidly in these doses. Seventy-five micrograms clonidine was as effective as 150 µg clonidine; thus, it would seem a preferable dose for most patients.

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## CLONIDINE AND KETANSERIN FOR SHIVERING

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