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 α2-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 μg 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 μg.

Results: The duration of shivering was significantly shorter in those given clonidine (2.1 ± 0.9 min) than in the other two groups and shorter in the ketanserin group (4.3 ± 0.9 min) than in the saline group (12.0 ± 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 μg clonidine was no more effective than saline. Two minutes after treatment, 150 μg obliterated shivering in all patients. Five minutes after treatment, all patients given 75 μg had stopped shivering. Systolic arterial pressure and heart rate decreased significantly in patients given 75 and 150 μg clonidine.

Conclusions: Clonidine (150 μg) and ketanserin (10 mg) both are effective treatment for postanesthetic shivering. The effect of clonidine on shivering is dose-dependent; whereas 37.5 μg had no effect, 75 μg clonidine stopped shivering within 5 min. (Key words: Anesthetic complications; shivering. Sympathetic nervous system, α2-adrenergic agonist: clonidine. Sympathetic nervous system, 5-HT2 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, 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 α2-adrenergic receptor agonist, and ketanserin, a 5-hydroxytryptamine (5-HT2) receptor antagonist, each reportedly reduce postanesthetic shivering. Furthermore, clonidine apparently prevents postanesthetic shivering when administered before or during surgery. 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. Additionally, both clonidine and ketanserin can induce undesirable hemodynamic changes, such as hypotension. Accordingly, we compared the effects...
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% N₂O 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. Oscillographic arterial blood pressure, heart rate (Cardiogap, 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. Oscillographic 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.8 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 ± 0.9 min, ketanserin = 4.3 ± 0.9 min, and saline = 12.0 ± 1.6 min (median values: saline 12

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

<table>
<thead>
<tr>
<th></th>
<th>Isotonic Saline</th>
<th>Clonidine</th>
<th>Ketanserin</th>
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<tbody>
<tr>
<td>Age (yr) (mean ± SD)</td>
<td>41 ± 16</td>
<td>38 ± 15</td>
<td>34 ± 9</td>
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<tr>
<td>Gender: M/F</td>
<td>12/7</td>
<td>12/3</td>
<td>15/5</td>
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<tr>
<td>Isoflurane</td>
<td>5</td>
<td>3</td>
<td>7</td>
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<tr>
<td>Enflurane</td>
<td>11</td>
<td>11</td>
<td>11</td>
</tr>
<tr>
<td>Halothane</td>
<td>3</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Propofol</td>
<td>0</td>
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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 ± 0.8° C, clonidine 35.5 ± 0.6° C, and ketanserin 35.6 ± 0.8° 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. 2.** Change in core temperature (mean ± SEM) in shivering patients treated by an intravenous bolus of isotonic saline (△), 10 mg ketanserin (○), or 150 μg clonidine (●). SEMs of the K group were omitted for clarity (SEM ranged from 0.05° to 0.12° 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-μg dose of clonidine stopped shivering in all the patients within 2 min. Two minutes after injection of 75 μg 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 μg 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 μg clonidine than after saline or 37.5 μg clonidine, but no significant differences were detected between the 75 and 150 μg groups. Heart rate did not differ significantly among the groups (fig. 3).

**Discussion**

Our data confirm that both 150 μg 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 μg clonidine administered as an intravenous bolus is sufficient to treat postanesthetic shivering.
Table 2. Effect of Isotonic Saline, 10 mg Ketanserin, and 150 µg Clonidine on Heart Rate and Arterial Pressure

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

Data are mean ± 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 µg clonidine (C).

Nalda et al. 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. Subsequent stimulation of cutaneous cold receptors contributes to maintenance of shivering. Nalda et al. hypothesized that vasodilation induced by ketanserin increases skin temperature 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 µg/kg clonidine over 1 h or over 3 h 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, µg clonidine. However, the initial report showed that an intravenous bolus of 150 µg clonidine dramatically reduced or abolished shivering. Prevention of postoperative shivering by clonidine given before or during anesthesia also has been proposed. 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. 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 a2 and α1 adrenoceptors. However, vasoconstriction would reduce skin temperature, stimulate cutaneous cold thermo-

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

<table>
<thead>
<tr>
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<th>Dose of Clonidine (µg)</th>
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<tr>
<td>Age (yr) (mean ± SD)</td>
<td>31 ± 15</td>
</tr>
<tr>
<td>Gender: M/F</td>
<td>8/2</td>
</tr>
<tr>
<td>Enflurane</td>
<td>6</td>
</tr>
<tr>
<td>Halothane</td>
<td>1</td>
</tr>
<tr>
<td>Isoflurane</td>
<td>3</td>
</tr>
</tbody>
</table>

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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.15 Finally, the density of α2-adrenergic receptors is high in the hypothalamus.14 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 α adrenoceptors than serotoninergic receptors.1-6,13-17 Furthermore, it is likely that new, highly specific α2-agonist agents, such as dexmedetomidine17 and mivazerol,18 soon will be available clinically.

Patients respond to core hypothermia with vasoconstriction and shivering thermogenesis.19 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.13 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,

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 ± 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.
these patients may require active treatment of hypo-
thermia to prevent its continuing side effects, including
prolonged duration of drug action, impaired coagu-
lation, negative nitrogen balance, and possibly, risk
of infection. Consequently, maintaining perioperative
normothermia is preferable to postoperative treat-
ment of shivering.

Shivering is associated with vasoconstriction as well
as increases in heart rate and arterial blood pressure. Not
surprisingly, treatment of shivering reverses these
hemodynamic changes. However, clonidine per se
contributes to this reversal; systolic arterial blood pres-
sure and heart rate were significantly lower in patients
treated with clonidine than in those given saline, even
after cessation of shivering. The hemodynamic conse-
quences of effective doses of clonidine and ketanserin
are beneficial for shivering patients, rather than dele-
terious. 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 clo-
nidine is administered to hypovolemic patients.

Both clonidine and ketanserin have terminal half-lives
exceeding 10 h. After the rapid distribution phase
following intravenous injections, their plasma concen-
trations remain relatively high and nearly constant for
a longer period than required for these studies.

Our study does not allow us to determine what con-
stitutes the best treatment for postanesthetic shivering.
Meperidine is considered to be the drug of choice for
the treatment of shivering in spontaneously breathing
patients. Inclusion of a meperidine group as a pos-
tive control and a dose-response study with ketanserin,
therefore, would have been appropriate to compare
the different pharmacologic agents. Intravenous ad-
ministration of 25–50 mg meperidine reduces or abol-
ishes postoperative shivering in 50–60% of pa-

tients. 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 respi-
ratory depression after small doses of meperidine, al-
though small, is increased when repeated doses are
given.

Clonidine contributes to pain relief without poten-
tiating opioid-induced respiratory depression. The
sedative effect of clonidine is not necessarily undesirable
in the immediate postoperative period, particu-
larly after invasive surgical procedures producing dis-
comfort. Finally, in addition to all these pharmacologic
treatments associated with potential side effects, skin-
surface warming also is effective in treating postanes-
esthetic shivering 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-µg
bolus was almost as effective as the 150-µg 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 ac-
tivity mediated by stimulation of spinal and supraspin-
α2 and/or imidazoline receptors. Moreover, plasma
concentrations of clonidine are not linearly related to
the dose of clonidine, and biphasic responses of ar-
terial blood pressure have been observed also.
Fur-
thermore, transient hypertension due to stimulation of
vascular α2-adrenergic receptors has been reported
when an intravenous bolus of clonidine is adminis-
tered. However, we, and others, 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 he-
modynamic difference between patients given 75 and
150 µg clonidine. Since shivering per se causes hyper-
tension and tachycardia, inclusion of shivering at dif-
ferent intensities might have obscured hemodynamic
differences between patients given 75 and 150 µg clo-
nidine.

Although quantification of shivering by oxygen con-
sumption 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 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

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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.

References


