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# Oral clonidine reduces thiamylal requirement for induction of anesthesia in adult patients

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**Abstract:** Although preanesthetic clonidine, an α-2 agonist, is known to reduce anesthetic requirements, the effect of preanesthetic oral clonidine medication per se on the requirement of thiamylal in adult humans has not yet been examined. One hundred and sixty-one adult patients (14–78 years of age) were randomly assigned to groups that received oral clonidine (5 μg·kg$^{-1}$ ($n$ = 51), 2.5 μg·kg$^{-1}$ ($n$ = 55), or none ($n$ = 55)) in addition to 20 mg oral famotidine 90 min before anesthesia induction. Thiamylal was injected at the rate of 25 mg every 15 s until the eyelash reflex disappeared, while blood pressure and heart rate were recorded at 30-s intervals from the start of the induction. Thiamylal requirements were significantly less in both clonidine groups (2.95 ± 0.09 and 3.14 ± 0.10 mg·kg$^{-1}$ (mean ± SE) for patients receiving 5 μg·kg$^{-1}$ and 2.5 μg·kg$^{-1}$ clonidine, respectively) than in the control group (3.81 ± 0.11 mg·kg$^{-1}$, $P < 0.05$); however, no difference was found between the two clonidine groups. Although mean blood pressure and heart rate during the study period were significantly lower in both clonidine groups than in the control group, no profound hypotension or marked bradycardia were noted in the clonidine groups.

**Key words:** Thiamylal, Oral clonidine, Alpha-2 adrenergic agonists

## Introduction

Preanesthetic oral administration of clonidine, a partial α-2 adrenergic agonist, has been reported to reduce intraoperative anesthetic requirements for opioids [1–3], droperidol [4], and volatile anesthetics [1,5,6]. Likewise, intravenous clonidine [7] and oral clonidine with diazepam [8] reduced thiopental requirement for induction of anesthesia in adults. Recently, it has been shown that preanesthetic administration of 2 μg·kg$^{-1}$ or 4 μg·kg$^{-1}$ oral clonidine reduce thiamylal requirement in children in a dose-dependent manner by approximately 17% and 37%, respectively [9]. However, it remains to be proved whether oral clonidine premedication per se would affect the induction dose of thiamylal in adults.

The purpose of the current randomized study was to evaluate the dose-related effect of oral clonidine preanesthetic medication on the thiamylal requirement for anesthesia induction in adult patients. We also examined the combined effect of oral clonidine and intravenous thiamylal on hemodynamics during the induction of anesthesia.

## Materials and methods

One hundred and sixty-one patients, ASA physical status I or II, ranging in age from 14 to 78 years, and scheduled to have general anesthesia for elective surgeries were selected for this study. The study protocol was approved by our local ethical committee on clinical investigation, and written informed consent was obtained from each patient. None of the patients had taken any medication affecting the central nervous system such as benzodiazepines, tricyclic antidepressants, or other α-2 adrenergic agonists such as naphazoline nitrate or methyldopa, within the last 10 days. In addition, obese patients whose body mass index (BMI: weight (kg)/{height (m)}$^2$) was larger than 27 were excluded from this study.

Patients were randomly assigned to one of three groups. The 5 μg·kg$^{-1}$ clonidine group (C-5, $n$ = 51) and the 2.5 μg·kg$^{-1}$ clonidine group (C-2.5, $n$ = 55) received approximately 5 μg·kg$^{-1}$ and 2.5 μg·kg$^{-1}$ clonidine, respectively, plus 20 mg famotidine orally 90 min before anesthesia induction, whereas the control group ($n$ = 55) received 20 mg famotidine alone.

After arrival at the operating room, one of authors checked the sedation score, which was graded 0–5

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(0, very excited; 1, alert, tense, and inquisitive; 2, sedated, but not sleepy, with eyes open; 3, eyes sometimes open and looking sleepy to observers, although the patient herself or himself does not complain of sleepiness; 4, eyes closed almost continuously and complains of sleepiness; 5, drowsy and almost no response to verbal commands) [10]. A 16 G intravenous cannula was placed in a forearm vein for continuous infusion of lactated Ringer's solution at a rate of $10 ml \cdot kg^{-1} \cdot h^{-1}$. Thereafter, continuous monitoring of the electrocardiogram and noninvasive recordings of blood pressure (BP) and heart rate (HR) with an automated oscillometric device (Nippon Colin 203Y, Tokyo, Japan) were established. A pulse oximeter (Nippon Koden OLV-1100, Tokyo, Japan) was attached to the patient's index finger.

After baseline BP and HR were recorded, 2.5% thiamylal solution (Isozol, Yoshitomi, Osaka, Japan) was injected intravenously at a rate of 25 mg every 15 s until the eyelash reflex disappeared [11]. The eyelash reflex was assessed at intervals of 15 s by independent anesthesiologists who were unaware of the study drug and the dose of injected thiamylal. BP and HR were recorded at 30 s intervals from the start of the injection of thiamylal to loss of the eyelash reflex. After confirmation of loss of eyelash reflex, the face mask was applied, and the anesthetic technique was conducted as indicated for the surgery. When mean BP $<$ 50 mmHg and HR $<$ 40 beats$\cdot$min$^{-1}$ were noted, 5–10 mg ephedrine and 0.5 mg atropine, respectively, were administered intravenously.

Values are given as mean ± standard error (SE). Statistical comparisons among groups were performed using two-way analysis of variance (ANOVA) with the Fisher test. The Mann–Whitney $U$-test was used to compare the sedation scores among groups. $P$ values less than 0.05 were considered to be statistically significant.

## Results

There were no differences among the three groups with respect to age, gender, height, and weight (Table 1). Although sedation scores were significantly greater in both clonidine groups (2.47 ± 0.08 and 2.29 ± 0.07 for C-5.0 and C-2.5 groups, respectively) than in the control group (2.02 ± 0.04, $P < 0.05$), there was no significant difference between the two clonidine groups.

Thiamylal requirements were significantly less in both clonidine, groups (2.95 ± 0.09 and 3.14 ± 0.10 mg$\cdot$kg$^{-1}$ for patients receiving 5 μg$\cdot$kg$^{-1}$ and 2.5 μg$\cdot$kg$^{-1}$ clonidine, respectively) than in the control group (3.81 ± 0.11 mg$\cdot$kg$^{-1}$, $P < 0.05$). However, thiamylal requirements were comparable between C-5.0 and C-2.5 groups (Fig. 1).

Although mean BP and HR were significantly lower in both clonidine groups than in the control group before and during anesthesia induction (Figs. 2 and 3), no profound hypotension (mean BP $<$ 50 mmHg) or bradycardia (HR $<$ 40 beats$\cdot$min$^{-1}$) were noted. Therefore, no patients received intravenous ephedrine or atropine during anesthesia induction. Also, arterial oxygen saturation was maintained above 95% during induction of anesthesia in all patients.

## Discussion

The present results show that oral clonidine premedication reduced thiamylal requirements for anesthesia induction and produced neither marked hypotension nor bradycardia during anesthesia induction in adult patients. However, thiamylal requirement was decreased to the same extent in patients receiving either 5.0 or 2.5 μg$\cdot$kg$^{-1}$ clonidine.

According to several previous reports, intravenously administered clonidine (0.6–5.0 μg$\cdot$kg$^{-1}$), alone or with 20 mg oral temazepam premedication, reduced the dose of thiopental required to induce anesthesia by 15%–37% in adult patients [7,12]. Similarly, preanesthetic medication with 225–375 μg oral clonidine (approximately 3.5–4.7 μg$\cdot$kg$^{-1}$) plus 5–15 mg diazepam reduced thiopental requirements by approximately 20% in adult humans [8]. Our present results that 5.0 and 2.5 μg$\cdot$kg$^{-1}$ oral clonidine reduced thiamylal requirements by 23% and 18%, respectively, agree with those of Orko et al. [8]. However, we observed a smaller reduction in barbiturate requirements than had been reported previously

**Table 1.** Demographic data

| Group | Control ($n$ = 55) | C-2.5 ($n$ = 55) | C-5.0 ($n$ = 51) |
|---|---|---|---|
| Clonidine dose (μg$\cdot$kg$^{-1}$) | 0 | 2.53 ± 0.04 | 4.86 ± 0.07 |
| Age (years) | 46 ± 2 (14–77) | 44 ± 2 (16–78) | 43 ± 2 (18–69) |
| Gender (male/female) | 35/20 | 27/28 | 32/19 |
| Height (cm) | 159 ± 1 (139–180) | 160 ± 2 (139–183) | 160 ± 1 (148–178) |
| Weight (kg) | 55 ± 1 (40–75) | 58 ± 1 (32–77) | 56 ± 1 (41–84) |
| Hypertensive patients* | 6 | 7 | 5 |

Values are mean ± SE, with ranges in parentheses.
* Number of patients who were diagnosed as having hypertension and treated with antihypertensive agents.

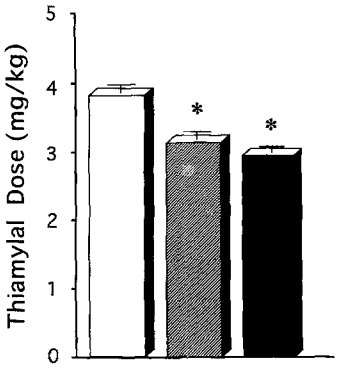


**Fig. 1.** Thiamylal requirements (mean ± SE) for induction of anesthesia in patients receiving no clonidine (*white column*, control, $n = 55$), 2.5 μg·kg$^{-1}$ clonidine (*shaded column*, C-2.5, $n = 55$), and 5.0 μg·kg$^{-1}$ clonidine (*black column*, C-5.0, $n = 51$). *$P < 0.05$ compared with control group

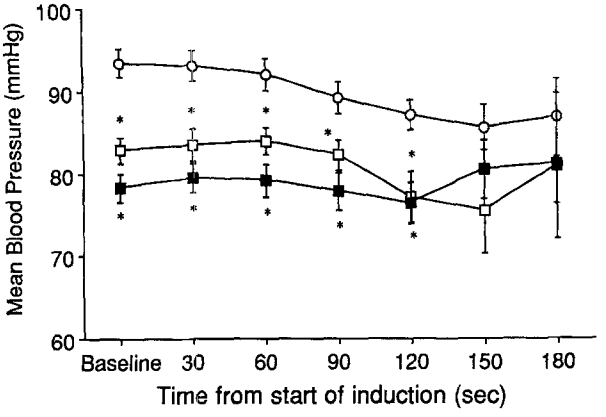


**Fig. 2.** Mean blood pressure (mean ± SE) before and during induction of anesthesia in patients receiving no clonidine (*open circles*, control, $n = 55$), 2.5 μg·kg$^{-1}$ clonidine (*open squares*, C-2.5, $n = 55$), and 5.0 μg·kg$^{-1}$ clonidine (*solid squares*, C-5.0, $n = 51$). *$P < 0.05$ compared with control group

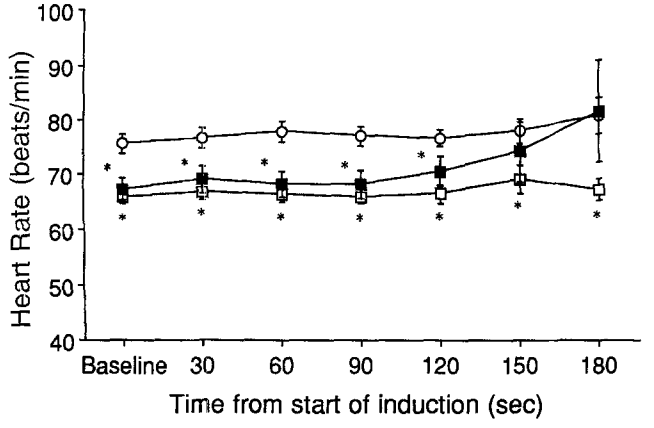


**Fig. 3.** Heart rate (mean ± SE) before and during induction of anesthesia in patients receiving no clonidine (*open circles*, control, $n = 55$), 2.5 μg·kg$^{-1}$ clonidine (*open squares*, C-2.5, $n = 55$), and 5.0 μg·kg$^{-1}$ clonidine (*solid squares*, C-5.0, $n = 51$). *$P < 0.05$ compared with control group

[7,9,12]. This finding was presumably due partly to differences in the route of clonidine administration and the patients' ages. Since the thiopental requirement until loss of the eyelash reflex by an incremental administration was reported to be significantly larger than that by a bolus administration [13], the thiamylal requirement may have been less than that in our results if administered as a bolus.

The present results that mean BP and HR in both clonidine groups were significantly lower than those in the control group before and during anesthesia induction are in agreement with those of Filos et al. [14]. However, in previous reports [7,9] there were no significant differences in BP and HR between clonidine and control groups after administration of barbiturate. These divergent findings are likely to be ascribed to the fact that the average patient's age in our study was higher than that in other studies [7,9]. Moreover, there were some hypertensive patients in our study groups, whereas such patients were excluded from previous research. Since the hypotensive effect of clonidine in normotensive patients is considered to be less than that in patients with hypertension [15], the inclusion of hypertensive patients in our study may have contributed to the difference in BP response. As shown in Fig. 2 and 3, mean BP and HR values were comparable between the control and clonidine groups at 150 and 180 s after the start of anesthesia induction. This may be due to the decreased sample size of patients studied and the wide individual variability in BP and HR values, because in most patients hemodynamic measurements were completed within 120 s when the eyelash reflex disappeared.

We examined the effect of two different doses of clonidine premedication upon thiamylal requirement in this study. However, there were no differences in thiamylal requirements for anesthesia induction, the hemodynamic effect, or sedative effects between C-5.0 and C-2.5 groups. This finding appears to be in agreement with a recent study demonstrating the existence of a ceiling effect in the clonidine-induced reduction of isoflurane requirement [16]. On the other hand, it has been shown that the degree of sedation correlated positively with plasma concentration of clonidine up to 1.5–2.0 ng·ml$^{-1}$ [17], and that plasma clonidine concentration of approximately 1 ng·ml$^{-1}$ was achieved following oral administration of 5 μg·kg$^{-1}$ clonidine [18]. Hence, in the present study plasma clonidine concentration seemed to be around or below 1 ng·ml$^{-1}$ in the clonidine groups, and different plasma concentrations of clonidine between C-5.0 and C-2.5 groups are unlikely to account for the present results that thiamylal requirements were not different between the two clonidine groups. Although the precise mechanism for the anesthetic-sparing effect of clonidine and for its

ceiling remains to be fully elucidated, a decrease in central noradrenergic transmission may contribute in part to this mechanism [19]. Furthermore, there is an investigation showing a profound reduction in anesthetic requirements with dexmedetomidine, a more specific and selective α-2 adrenergic agonist, thus raising the possibility that α-2 adrenergic agonists may be considered as anesthetic agents when administered alone [20]. Alternatively, this finding could be explained by pharmacokinetic alterations of barbiturate following administration of an α-2 agonist, since dexmedetomidine has been shown to decrease thiopental distribution volume and clearance [21].

In conclusion, preanesthetic oral clonidine at $5.0\,\mu g \cdot kg^{-1}$ or $2.5\,\mu g \cdot kg^{-1}$ reduces thiamylal requirements for induction of anesthesia in adult patients to a similar extent.

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