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## Oral Clonidine Premedication Does Not Alter the Efficacy of Simulated Intravenous Test Dose Containing Low Dose Epinephrine in Awake Volunteers

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**Background:** Clonidine premedication modifies the hemodynamic responses to sympathomimetics. The present study was designed to test whether clonidine altered the response to a small intravenous dose of epinephrine, such as that which might be used in an epidural test dose.

**Methods:** In 18 healthy volunteers, four series of determinations were performed in random order and were separated by a minimum 72 h: (1) no premedication followed by intravenous saline 3 ml, (2) no premedication followed by intravenous test dose containing 3 ml of 1.5% lidocaine + 15 µg epinephrine, (3) oral clonidine (5 µg/kg 1.5 h before hemodynamic determinations) followed by intravenous saline, and (4) oral clonidine followed by intravenous epinephrine-containing test dose. Systolic blood pressure (SBP) and heart rate (HR) were measured continuously, and symptoms associated with central nervous system toxicity were noted.

**Results:** After the test dose injections, HR and SBP increased with or without clonidine premedication. The 95% confidence intervals for the maximum HR increases with and without clonidine were 49-61 and 44-54 beats/min, respectively, indicating that one could not be absolutely certain that everyone would develop a positive HR response. The HR increase was  $\geq 20$  beats/min in 18 of 18 volunteers given epinephrine with or without clonidine and in 0 of 18 volunteers given saline. Calculated sensitivities, specificities, and positive and negative predictive values were all 100% based on the conventional HR criterion and were unaltered by clonidine. Subjective symptoms were not affected by clonidine.

**Conclusions:** Oral clonidine does not alter the efficacy of epinephrine-containing test doses used for detecting intravascular injection. (Key words: Anesthesia technique: epidural; test dose. Anesthetics, local: lidocaine. Complications: intravascular injection. Sympathetic nervous system: epinephrine;  $\alpha_2$ -adrenergic agonists; clonidine.)

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CLONIDINE, a selective  $\alpha_2$ -adrenergic agonist, is increasingly used as an anesthetic adjuvant.<sup>1</sup> It provides preoperative sedation, reduces intraoperative anesthetic requirement, and potentiates postoperative analgesic regimen.<sup>1</sup> Clonidine has been shown to increase pressor responses to peripherally acting sympathomimetics such as ephedrine,<sup>2</sup> phenylephrine,<sup>3</sup> and heart rate (HR) response to isoproterenol.<sup>4</sup> However, modulation by clonidine of hemodynamic responses to intravenously administered epinephrine has not been determined. Investigating blood pressure (BP) and HR responses to epinephrine has been important clinically because small doses of epinephrine are used in an epidural test dose for detecting accidental intravascular injection. Accordingly, the present study was designed to determine effects of oral clonidine premedication on hemodynamic responses to and the efficacy, *i.e.*, sensitivity, specificity, and positive (+PV) and negative predictive values (-PV), of simulated intravenous test dose based on the conventional HR and systolic blood pressure (SBP) criteria previously determined from awake, nonpregnant, unmedicated volunteers.<sup>5</sup>

### Materials and Methods

A power analysis based on a previous report revealed that more than 16 volunteers would provide a power greater than 0.8 ( $P = 0.05$ ) for detection of 25% difference in paired hemodynamic responses.<sup>5</sup> After the study protocol was approved by our local ethics committee and informed consent was obtained, 18 nonpregnant, American Society of Anesthesiologists' (ASA) physical status I volunteers were enrolled in our study. All volunteers were free of cardiovascular disorders, did not take medications affecting cardiovascular system, did not consume alcoholic beverages daily, and abandoned caffeine-containing beverages for at least 48 h before the study.

After 8 h of fasting, an intravenous catheter was inserted at either forearm using local anesthetic infiltration, and lactated Ringer's solution was infused at a constant rate of  $5 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ . Standard lead II electrocardiography (ECG) and arterial tonometric BP (Nihon Colin, BP-508<sup>TM</sup>, Aichi, Japan) were applied at the contralateral arm. Then, each subject was allowed to rest supine for at least 20 min in a quiet environment before initiation of the study. In each subject, four series of determinations were performed in random order and separated by a minimum of 72 h; (1) no premedication followed by intravenous saline 3 ml, (2) no premedication followed by intravenous test dose consisting of 1.5% lidocaine 3 ml plus  $15 \mu\text{g}$  epinephrine (1:200,000), (3) oral clonidine (Boehringer Ingelheim, Hyogo, Japan, each tablet contains  $75 \mu\text{g}$ ) approximately  $5 \mu\text{g}/\text{kg}$  1.5 h before hemodynamic determination followed by intravenous saline 3 ml, and (4) oral clonidine followed by intravenous test dose of the same contents. The study drug was injected over 3 s into the intravenous catheter, and SBP and HR were continuously recorded for 5 min. HR and SBP were analyzed at 20-s intervals. In addition, maximum HR and SBP responses and any arrhythmia or ST-T changes on ECG were noted. At the completion of each determination, presence of any subjective symptom was recorded by an observer. Subjects were asked specifically if they had any perception of funny or metallic taste, dizziness, and tinnitus.

The study solutions were prepared and coded by the hospital pharmacy, and on completion of the study and data collection, the codes were broken by one of the authors (M.T.). Therefore, investigators observing hemodynamic changes and subjects were blinded to the content of the study solutions.

We have prospectively defined an increase in HR to be clinically significant (HR criterion) if it was more than or equal to 20 beats/min according to the study by Guinard *et al.*,<sup>5</sup> in which criterion was determined from unmedicated, nonpregnant, awake volunteers. Similarly, an increase in SBP greater than or equal to 15 mmHg was considered a positive response (SBP criterion). *Sensitivity* was defined as the number of true-positives divided by the number of true-positives plus false-negatives; *specificity* is the number of true-negatives divided by the number of true-negatives plus false-positives; *+PV* is the number of true-positives divided by the number of true-positives plus false-positives; *-PV* is the number of true-negatives divided by the number of true-negatives plus false-negatives.

All data are presented as mean  $\pm$  SD. Comparisons of

maximum changes in HR and SBP after the epinephrine-containing test dose with or without clonidine were performed using paired Student's *t* test. Occurrence of subjective symptoms were compared with chi-square test. A *P* value less than 0.05 was considered the minimum level of statistical significance.

## Results

There were 4 men and 14 women. The mean age, weight, and height were  $22 \pm 1$  yr,  $53 \pm 6$  kg, and  $160 \pm 5$  cm, respectively. The mean clonidine dose was  $4.97 \pm 0.28 \mu\text{g}/\text{kg}$ . Baseline (preinjection of the test dose) SBP, diastolic blood pressure (DBP), and HR after clonidine ( $101 \pm 10$  mmHg,  $53 \pm 6$  mmHg, and  $53 \pm 5$  beats/min, respectively) were significantly less than those without clonidine ( $114 \pm 9$  mmHg,  $62 \pm 5$  mmHg, and  $66 \pm 5$  beats/min, respectively;  $P < 0.01$ ). No significant difference was seen in SBP, DBP, and HR before saline injections from those before test dose injections with or without clonidine (data not shown).

Intravenous injection of the test dose containing epinephrine caused increases in HR and SBP with and without clonidine (fig. 1). Mean maximum increases in HR and SBP were significantly greater after clonidine ( $55 \pm 12$  vs.  $49 \pm 10$  beats/min and  $43 \pm 14$  vs.  $33 \pm 12$  mmHg, respectively), although no significant difference was seen in absolute values of HR and SBP achieved. Intravenous saline caused no significant changes in HR and SBP at any interval with or without clonidine.

All volunteers given epinephrine-containing test dose developed HR increases more than or equal to 20 beats/min regardless of whether clonidine had been given. No volunteers given saline developed a HR increase of more than or equal to 20 beats/min. Hence, sensitivity, specificity, *+PV*, and *-PV* were all 100%. However, based on the SBP criterion, sensitivities, specificities, *+PVs*, and *-PVs* were 94%, 83%, 85%, and 94% with clonidine and 94%, 89%, 89%, and 94% without clonidine.

All volunteers were sedated 1.5 h after clonidine medication. Incidence of tinnitus, funny or metallic taste, and dizziness were present in 10, 3, and 6 subjects with clonidine, and in 13, 2, and 7 subjects without clonidine ( $P > 0.05$ ). No arrhythmia or ST-T changes were observed in any patient throughout the study.

## Discussion

The major finding of the present study is that oral clonidine premedication,  $5 \mu\text{g}/\text{kg}$ , does not affect the

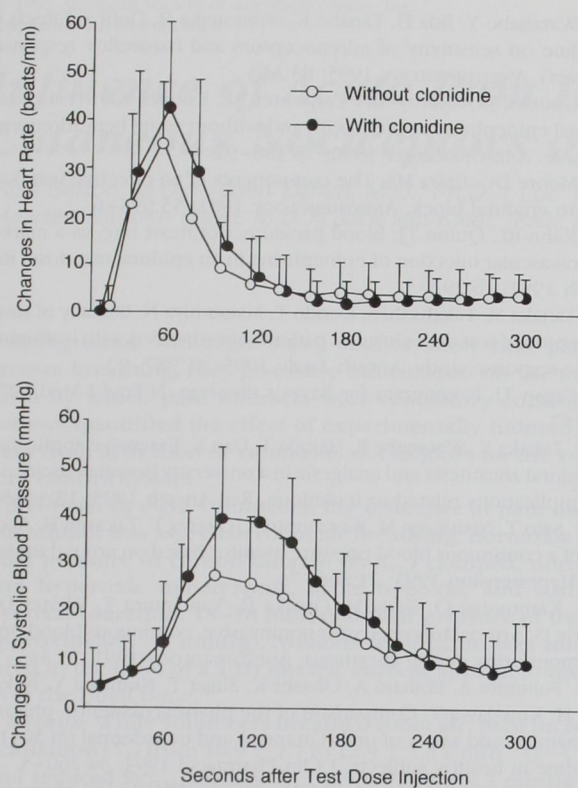


Fig. 1. Changes in heart rate (top panel) and systolic blood pressure (bottom panel) after intravenous injection of an epidural test dose containing 15  $\mu$ g epinephrine and 45 mg lidocaine with and without clonidine premedication 5  $\mu$ g/kg. Since heart rates and systolic blood pressure were essentially unchanged after 3 ml saline injection, these data are not presented. Data are mean  $\pm$  SD.

reliability of the standard epidural test dose for detecting intravascular injection based on the conventional HR criterion. We also have shown that the BP and HR responses to intravenous epinephrine, 15  $\mu$ g, were increased by oral clonidine in healthy subjects. Since Moore and Batra reported detectable HR increases after local anesthetic with 15  $\mu$ g epinephrine,<sup>6</sup> such a combination to detect intravascular migration of the epidural catheter has become a standard anesthetic practice. Guinard *et al.*<sup>5</sup> demonstrated that an increase in HR  $\geq$  20 beats/min was 100% sensitive and specific for intravascular injection in healthy, unmedicated, non-pregnant adult volunteers. Our data have shown that in clonidine-treated subjects, the 95% confidence interval for the maximum HR change after intravenous test dose was 49–61 beats/min with clonidine, indicating that the testing regimen for the conventional HR criterion is also applicable, but one cannot be absolutely

certain that everyone will develop a HR increase  $\geq$  20 beats/min.

In contrast, reliability of the SBP criterion (positive if  $\geq$  15 mmHg increase) may be marginal in awake healthy subjects with or without clonidine. The SBP criterion was reported to be more sensitive than HR criterion in some clinical situations, such as in the elderly population,<sup>7</sup> in patients on  $\beta$ -blockers,<sup>5</sup> and during general anesthesia.<sup>8</sup> The +PV and -PV can be used to examine the actual usefulness of the test results according to Bayes' theorem,<sup>9</sup> which gives conditional probability adjusted for the observed prevalence of the phenomenon, *i.e.*, intravascular catheterization in the context of our study. When such incidence is considered 0.7% according to a recent report,<sup>10</sup> the actual +PV and -PV after application of Bayes' theorem were found to be 5% and  $>$  99.9% with clonidine, and 7% and  $>$  99.9% without clonidine. These results imply that in clinical situations, 95% of epidural catheters with clonidine and 93% without clonidine may be unnecessarily removed when the clinical judgment is solely based on the peak SBP, indicating the limited value of positive test results.

It is not clear from our study why hemodynamic response to a small dose of intravenous epinephrine was increased by a single oral dose of clonidine. Similar findings were reported in ephedrine,<sup>2</sup> phenylephrine,<sup>3</sup> norepinephrine,<sup>5</sup> and isoproterenol.<sup>4</sup> We cannot exclude a possibility that up-regulation of adrenoceptors might have occurred as sympathetic nervous system activity and circulating plasma catecholamine concentrations decreased by clonidine treatment.

A possible criticism of our investigation is that the SBP changes determined by arterial tonometry may not be accurate measurements of BP compared with the measurements by an invasive method. However, the tonometric SBP and the intraarterial SBP corresponded well in normotensive and hypertensive patients<sup>11</sup> for the range of pressure<sup>12</sup> as seen in our study. We have no reason to question the reliability of tonometric BP in healthy young subjects with no evidence of peripheral vascular abnormalities. The power of the study in relation to the sample size may be another limitation to its interpretation. However, significance is enhanced by our study design, which uses subjects as their own control for each series of injections. Lastly, we did not measure plasma clonidine concentration. However, previous pharmacokinetic studies have shown that plasma concentration increases rapidly after a single oral dose of clonidine and reaches almost 80% of the peak plasma

level after 1.5 h.<sup>13,14</sup> In addition, effects of clonidine medication clearly were seen in significantly depressed baseline hemodynamic variables and in sedated volunteers.

In conclusion, oral clonidine premedication, 5 µg/kg, increased BP and HR responses to an intravenously administered epinephrine-containing test dose in healthy awake volunteers. However, clonidine affected neither the efficacy based on the conventional HR criterion (sensitivity, specificity, +PV, -PV — all 100%) nor the incidence of subjective symptoms as a result of the test dose injection. Regardless of the presence of clonidine, the value of the SBP criterion was limited after a positive test result.

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