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Effects of Oral Clonidine Premedication on the Hypotensive Response to Nicardipine during Isoflurane and Nitrous Oxide Anesthesia

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Abstract

Since clonidine has a negative chronotropic effect and inhibits catecholamine release, it may blunt sympathetic-mediated heart rate acceleration secondary to vasodilation, thereby enhancing the hypotensive effect of vasodilators. In this study we examined whether preanesthetic clonidine medication would alter the hypotensive effect of nicardipine in surgical patients during general anesthesia.

After approval by the local ethical committee and informed consent, 60 surgical patients, ASA I, 24-67 yr, were selected for this study. The patients received oral clonidine approximately 5 μg/kg (clonidine-5 group, n=20) or 2.5 μg/kg (clonidine-2.5 group, n=19) 90 min before anesthesia, while the remaining 21 patients received no clonidine (control group). General anesthesia was induced with thiopental approximately 5 mg/kg, and maintained with an end-tidal concentration of isoflurane 0.3-0.9% and nitrous oxide 67% in oxygen after tracheal intubation. After obtaining hemodynamic stability, nicardipine 10 μg/kg was injected IV in 5 seconds. Blood pressure and heart rate were measured at 1-min intervals for 10 min following nicardipine. Data (mean±SD) were analyzed using ANOVA and Bonferroni's multiple-comparison test, with $P<0.05$ being significant.

There were no significant differences with respect to demographic and pre-nicardipine hemodynamic data. The maximum decreases in mean blood pressure following nicardipine did not differ among the three groups (−15±5, −13±5, −13±6 mmHg in the clonidine-5, clonidine-2.5, and control groups, respectively).

These results suggest that oral clonidine 2.5 or 5 μg/kg medication did not enhance the hypotensive effect of nicardipine in normotensive patients during isoflurane anesthesia.

Key words; hypotensive effect, nicardipine, oral clonidine premedication

Introduction

Nicardipine, one of commonly used drugs for deliberate hypotension, induces hypotension by selectively blocking calcium channels in the peripheral vasculature. Since physiological responses such as increases in heart rate, myocardial contractility and circulating catecholamine release occur during induced hypotension, inhibition of these alterations are likely to enhance the hypotensive effects of vasodilators. For instance, β-adrenoceptor blockade is advocated in combination with other vasodilators for potentiation of deliberate hypotension or reduced requirement of vasodilators[1~5].

α_2 agonists are known to exert a bradycardic effect by inhibiting noradrenaline release from peripheral prejunctional nerve endings[6], while central mediated bradycardic effect of α_2 agonists is well recognized to

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be due to suppression of sympathetic outflow and potentiation of parasympathetic nervous activity[6,7]. Thus, oral clonidine, an alpha2 agonist, premedication is likely to increase the risk of bradycardia as compared with other premedication[8~12]. Indeed, several clinical reports have implicated clonidine as causing a high-grade atrioventricular block or bradyarrhythmias during clonidine therapy for hypertension[13~16] or following clonidine overdose[17~20].

No clinical investigation has studied the hemodynamic interaction between clonidine and nicardipine in humans. The present study examined this proposition by evaluating the dose-related interaction between clonidine and IV nicardipine, and tested whether the hypotensive effect of nicardipine would be enhanced by oral clonidine premedication.

Methods

Sixty adult patients aged between 24 and 67 yr undergoing a variety of general surgical procedures classified as ASA physical class 1 or 2, were studied. The study was approved by our local ethics committee and written informed consent was obtained from each patient. All patients had normal sinus rhythms. Patients with a history of cardiovascular disorders, diabetes, disorders known to affect autonomic functions, and those taking medications known to affect cardiovascular functions were excluded.

The patients were randomly assigned (sealed envelopes) to one of the following three groups according to the dosage of clonidine. Patients of the control group (n=21) received no oral clonidine, whereas patients of the two clonidine groups received oral clonidine (Boehringer Ingelhaim Co., Ltd.) in a dose of approximately 2.5 μg/kg (n=19), or 5 μg/kg (n=20), in addition to 150 mg oral ranitidine (H2-blocker) 1.5–2 h before arrival in the OR.

On arrival in the OR, a 20-gauge IV cannula was inserted and lactated Ringer's solution was administered at an approximate rate of 20 ml/kg/hr throughout the study. Standard lead II electrocardiography and an automated blood pressure (BP) cuff at the contralateral arm were applied. HR was determined as an average of 4-sec intervals recorded on the electrocardiography (ECG) monitor, and BP was measured with an automated BP measuring device. BP and HR were measured at 1-min intervals during the study.

After breathing 100% oxygen, all patients received IV thiopental of approximately 5 mg/kg over 30 seconds and inspired concentration of 2% isoflurane for anesthesia induction. After tracheal intubation was facilitated with IV vecuronium approximately 0.2 mg/kg, general anesthesia was maintained with an end-tidal concentration of isoflurane 0.3–0.9% and 67% nitrous oxide in oxygen. Mechanical ventilation was performed to maintain Et-CO_2 at approximately 35 mmHg. If mean BP fell below 60 mmHg or HR below 50 beats/min, a rescue drug (ephedrine 0.1 mg/kg or atropine 10 μg/kg) was given. The patient was excluded from subsequent analysis.

After a stable hemodynamic state (mean BP and HR of more than 60 mmHg and 50 beats/min, respectively) was obtained, nicardipine 10 μg/kg was injected IV over 5 seconds in all patients. BP and HR were measured at 1-min intervals for 10 min following nicardipine before surgical stimulation. If patient's mean BP fell below 50 mmHg and HR below 50 beats/min, rescue treatment was given. The patient was then excluded from subsequent analysis. Immediately after the last measurements, arterial blood was sampled and analyzed for pHa, carbon dioxide tension ($PaCO_2$), oxygen tension (PaO_2), and base excess with a compact blood gas CO-Oximeter and electrolyte analyzer (GEM®PREMIER 400, Instrumentation Laboratory, United Kingdom).

Data were expressed as mean±standard deviation (SD). Patient characteristics were compared using analysis of variance (ANOVA) and unpaired student's t test. Student t-test with Bonferroni's correction was used for comparisons between groups, with $P<0.05$ being significant. Testing for significance in the incidence of hypotension among the three groups was accomplished by chi-squared analysis.

Table 1 Patient demographic characteristics and doses or end-expiratory concentration of anesthetic agents used during induction and maintenance of general anesthesia

Group	Clonidine-5 (n=18)	Clonidine-2.5 (n=14)	Control (n=19)
Age (year)	36±15	35±10	37±16
Weight (kg)	58±13	56±11	57±9
Height (cm)	162±10	159±8	163±8
Gender (M/F)	8/10	6/8	9/10
Clonidine dose (μg/kg)	4.96±0.23	2.55±0.17	−
Thiopental dose (mg/kg)	4.8±0.1	4.8±0.2	4.8±0.1
Vecuronium dose (mg/kg)	0.20±0.01	0.19±0.01	0.20±0.01
End-expiratory concentration of isoflurane (%)	0.33±0.11	0.41±0.23	0.39±0.19
Lactated Ringer's solution (ml/kg/h)	20.8±4.2	21.2±3.9	20.2±2.2

Values are mean±SD.

Table 2 Hemodynamic variables before nicardipine administration, and values of arterial blood gas analysis just after the last hemodynamic measurement

Group	Clonidine-5 (n=18)	Clonidine-2.5 (n=14)	Control (n=19)
Mean blood pressure (mmHg)	74±9	77±12	77±8
Heart rate (beats/minute)	60±6	66±14	65±9
pHa	7.46±0.03	7.47±0.04	7.46±0.04
$PaCO_2$ (mmHg)	35±4	33±4	34±4
PaO_2 (mmHg)	162±36	169±28	157±31
Base excess (mEq/L)	2.1±1.9	1.4±1.6	1.9±1.9

Values are mean±SD.

Results

Before nicardipine injection, two patients in the clonidine-5 group, five patients in the clonidine-2.5 group, and two patients in the control group required pharmacological management for hypotension because of mean BP of less than 60 mmHg. There were, however, no significant differences among the patients with large and medium doses of clonidine and the patients without clonidine in the incidence of hypotension. All of these hypotensive patients responded well to IV ephedrine 0.1 mg/kg. These patients were excluded from analysis. None of the patients had a HR of less than 50 beats/min.

There were no significant differences among the three groups of patients with respect to age, weight, height, ratio of men to women, doses of thiopental and vecuronium or concentrations given for induction and maintenance of isoflurane, infusion rate of lactated Ringer's solution prior to injection of nicardipine (**Table 1**). Clonidine doses in the clonidine-5 and clonidine-2.5 groups were 4.96±0.23 μg/kg and 2.55±0.17 μg/kg, respectively. Hemodynamic variables just before nicardipine administration, and values of arterial blood analysis immediately after the last hemodynamic measurement were similar among the three groups (**Table 2**).

In each group of patients, mean BP decreased below baseline values after nicardipine injection. The decreases of mean BP after nicardipine were maximal around 1–2 minutes after nicardipine administration, were sustained during the 10-minute study period in the three groups. But, the magnitudes of hypotensive responses to nicardipine in the three groups were comparable (**Fig. 1**). The HR increases above baseline values after IV nicardipine were not sustained

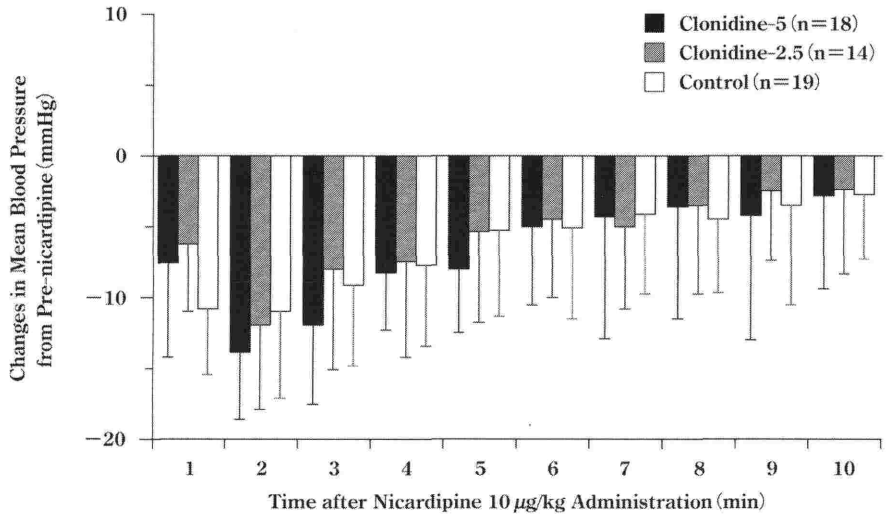

Figure 1 Changes in mean blood pressure after intravenous nicardipine 10 μg/kg in patients receiving oral clonidine of 0, 2.5 μg/kg, and 5 μg/kg
Values are mean±SD.
There was no statistically significant difference among the three groups.

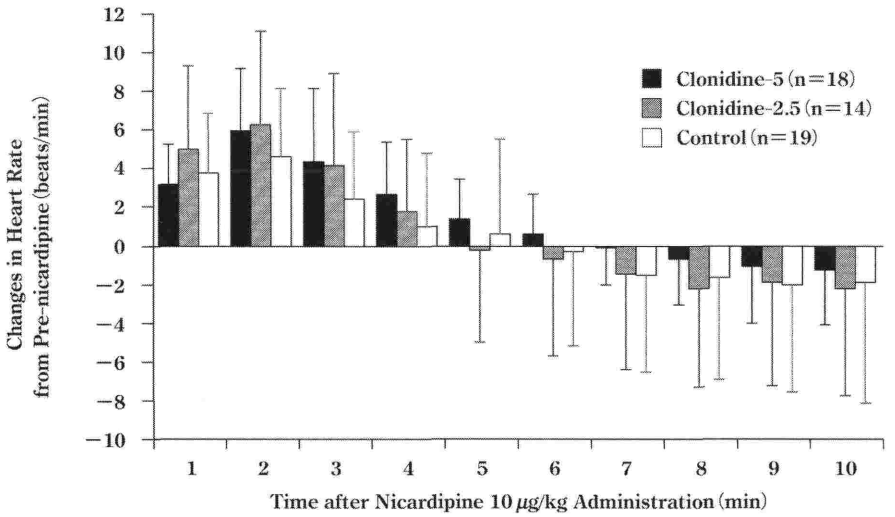

Figure 2 Changes in heart rate after intravenous nicardipine 10 μg/kg in patients receiving oral clonidine of 0, 2.5 μg/kg, and 5 μg/kg
Values are mean±SD.
There was no statistically significant difference among the three groups.

for longer than 6 minutes, and the thereafter HR decreased below baseline values in the three groups of patients (**Fig. 2**). The magnitudes of HR increases up to 4 minutes after nicardipine were similar, and subsequent HR decreases did not differ among the three groups.

No patient in each group developed any arrhythmia after nicardipine injection. There were no other adverse effects possibly related to large doses of clondine or to clonidine-nicardipine interaction.

Discussion

Our current results show that the hypotensive responses to IV nicardipine 10 μg/kg were not enhanced

in patients receiving oral clonidine 2.5–5 μg/kg premedication, as compared with patients given no clonidine premedication during isoflurane-nitrous oxide anesthesia. No detrimental effects related to clonidine or nicardipine, no increased incidence of hypotension due to clonidine before IV nicardipine, and no serious clonidine-nicardipine interaction were observed.

Although clonidine, a partial α2-adrenoceptor agonist, has been used for the primary aims of adequate sedation, reduced requirement of anesthetics and improved cardiovascular stability[12,21~26], clonidine premedication is likely to cause a greater incidence of hypotension and more frequent requirements of vasopressor agents[10]. However, the hypotensive episodes observed in this study may have been primarily ascribed to the vasodilatory effects of isoflurane[27], because the incidence of hypotension prior to IV nicardipine was similar among the clonidine and control groups.

Reflex tachycardia is a common occurrence after normalization of blood pressure in hypertensive patients treated with vasodilators[28]. But, the magnitude of reflex tachycardia seems to be lesser after nicardipine-induced hypotension when compared with other vasodilators[29]. Thus, we assumed that induction of deliberate hypotension by the use of nicardipine would be more smooth and efficacious, since the hypotensive effects of vasodilators are likely to be augmented by inhibition of hemodynamic and endocrine alterations associated with induced hypotension such as increases in heart rate, myocardial contractility and circulating catecholamine release[1~5].

However, in this study no potentiation of hypotensive effects of IV nicardipine 10 μg/kg was noted in patients receiving oral clonidine 2.5–5 μg/kg premedication. No enhancement of IV nicardipine-induced hypotension by clonidine premedication may be attributed to a weak negative chronotropic effect of oral clonidine 2.5–5 μg/kg as compared with β-adrenoceptor antagonists in the face of IV nicardipine-induced hypotension. In addition, IV nicardipine's vasodilatory effect might have been limited to a certain extent during isoflurane-nitrous oxide anesthesia, because peripheral vasculature might have been fully dilated during administration of isoflurane, a potent vasodilator[27]. Furthermore, the use of nitrous oxide in this study might account for no potentiation of hypotension after IV nicardipine, since nitrous oxide causes increases in plasma catecholamine levels[30,31], possibly resulting in masking clonidine's suppression of catecholaminie release.

There was no arrhythmia due to clonidine and nicardipine interaction in the present study. No increased occurrence of arrhythmia even after IV nicardipine in patients given oral clonidine would exclude the possibility of serious interaction between clondine and nicardipine.

In conclusion, oral clonidine 2.5 or 5 μg/kg medication did not enhance the hypotensive effect of nicardipine in normotensive patients during isoflurane and nitrous oxide anesthesia.

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