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Oral Clonidine Medication Partially Suppresses Transient Pressor Response to a Rapid Increase in Isoflurane Concentration

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Abstract

It is known that a rapid increase in isoflurane concentration elicits transient circulatory stimulation associated with plasma catecholamine elevations. Since clonidine, a relative selective α_2-agonist, inhibits release of catecholamine from the sympathetic nerve endings, the authors examined whether clonidine as an oral preanesthetic medication would suppress these hemodynamic and catecholamine responses. Twenty-five patients (aged 18－55yr) randomly received either oral clonidine approximately 5 μg/kg (n＝12) or no clonidine (n＝13). Following anesthesia induction and tracheal intubation with thiamylal 5 mg/kg and vecuronium 0.2 mg/kg iv, anesthesia was maintained with an end-tidal concentration of isoflurane (ET_{ISO}) of 1.3%, and a fresh gas flow of air 10 L/min plus oxygen 2 L/min via a semi-closed circuit system. A radial arterial catheter was placed for monitoring of arterial pressure (AP) and for blood sampling for plasma norepinephrine (NE) and epinephrine (E) assay. After stable anesthesia with ET_{ISO} of 1.3 % for 15 min, the ET_{ISO} was maintained at 2.6 % for 10 min by increasing the inspired concentration and adjusting the vaporizer setting. After increasing the concentration of isoflurane, AP and heart rate (HR) values were recorded every minute for 10 min, while plasma NE and E levels were measured at baseline and at 1, 2, 3, 5, and 10 min. Data collection was completed in 10 and 12 patients, since systolic AP decreased below 70 mmHg in 2 and 1 patients of the clonidine and control groups, respectively, within 1-4 min following abrupt increase in ET_{ISO} ($P>0.05$ in the incidence of hypotension between groups). Systolic and diastolic APs were lower in the clonidine group than the control group before abrupt ET_{ISO} elevation ($P<0.05$). Following rapid increase in isoflurane concentration, significant elevations from baseline values ($P<0.05$) were noted in systolic AP at 2-min recording (18±3 mmHg, mean±SE) and in diastolic AP at 1-min (12±3 mmHg) and 2-min recordings (16±3 mmHg) in the control group. However, the clonidine group did not show significant transient AP increases, and a significant difference between groups ($P<0.05$) was found only in diastolic AP changes from baselines at 1 min after the high isoflurane challenge. Although HR increased from baseline values in both groups for approximately 6 min after the high isoflurane challenge, the magnitudes of HR increases were similar between groups. Plasma NE levels and E levels were less in the clonidine group than the control group throughout the study, while plasma E levels were less in the clonidine group before and at 5 and 10 min after the high isoflurane exposure ($P<0.05$). However, they increased in all patients of both groups following

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abrupt increase in ET_{ISO}. In addition, no intergroup difference was observed in the magnitudes of increases in plasma NE and E levels. These results suggest that oral preanesthetic medication of clonidine 5 μg/kg medication partially attenuates the pressor response but does not suppress the heart rate and catecholamine responses to a rapid increase in isoflurane concentration.

Key words : Isoflurane, Oral clonidine, α2-adrenergic agonists, Epinephrine, Norepinephrine

Introduction

Several recent reports have shown that high concentration of volatile anesthetics such as isoflurane or desflurane causes sympathetic stimulation associated with plasma catecholamine elevations[1~7] However, the pressor and positive chronotropic responses are relatively short lived when concentration of isoflurane or desflurane is abruptly increased, despite sustained elevations of plasma catecholamine levels[1~3].

Improvement of hemodynamic stability is one of modifications provided by systemic administration of clonidine, a preferential α2-adrenegic agonist[8~11] . Since clonidine is known to inhibit norepinephrine release from the sympathetic nerve endings[12 ~ 14] and attenuate the sympathoadrenal responses[15], it is likely that clonidine could blunt the hemodynamic and catecholamine responses associated with a sudden increase in isoflurane concentration.

Therefore, the goal of the current study is to assess whether preanesthetic oral clonidine medication would suppress the hemodynamic and catecholamine responses to a rapid increase in isoflurane concentration in patients. Since a 5 μg/kg dose of clonidine is most commonly used for preanesthetic medication[16,17], we chose this dose to apply one of the two groups in the current study.

Methods

Twenty-five normotensive patients aged 18 − 55 yr, who were in ASA physical status 1 or 2, gave their informed consent to participate in research approved by Human Investigation Committee at the University of Tsukuba Hospital. The subjects scheduled for elective surgery for otorhinolaryngological, plastic, or orthopedic procedures were included. The subjects had neither medical history nor been taking any drugs. Those who had diabetes mellitus, serum electrolyte abnormalities, anemia, renal dysfunction, hypertension, sinus bradycardia (heart rate $<$ 60 beats/min), and obesity exceeding standard body weight by 20 % or more, were excluded from this study.

Subjects fasted for 8 hours before the operation. Each patient was randomly assigned to one of two groups. The patients received either oral clonidine approximately 5 μg/kg (clonidine group ; n = 12) or none (control group ; n = 13), in addition to famotidine 20 mg p.o., 90 min prior to arrival at operating room. Because in Japan clonidine is available only in 75- or 150-μg tablets (Catapres®, Boehringer Ingelheim & Tanabe, Kawanishi City, Hyogo), administration doses of clonidine were determined by choosing the closest doses calculated by multiplying 37.5 μg (one half of a tablet) as a unit. Prescription of preanesthetic drugs was performed by one of anesthesiologists who were in charge of each anesthetic case, while the anesthesiologist making the observations was blinded to the treatment drugs.

After an electrocardiogram monitor (Bioview F™, San-ei Instrument Co. Ltd., Tokyo), a blood pressure cuff (Listmini™, Nippon Colin Co. Ltd., Tokyo) and a pulse oximeter (Capnomac Ultima™, Datex, Helsinki, Finland) were established, a 16-G intravenous cannula was placed into the forearm cutaneous vein. Lactated Ringer's solution was thereafter infused at an approximate rate of 20 $ml \cdot kg^{-1} \cdot h^{-1}$ until the end of study. General anesthesia was induced with intravenous thiamylal 4 − 5 mg/kg and tracheal intubation was facilitated with intravenous vecuronium 0.2 mg/kg. Anesthesia was maintained with an end-tidal concentration of isoflurane (ET_{ISO}) of 1.3%, with the background gas flow 12 L/min composed of air 10 L/min plus oxygen 2 L/min *via* a semi-closed circuit system.

The lungs were mechanically ventilated to control arterial blood carbon dioxide tension (P_{ACO_2}) at approximately 30 mmHg. Continuous monitoring of expiratory gases was performed by a multi-gas analyzer (Capnomac Ultima™, Datex, Helsinki, Finland).

An arterial cannula was placed in the radial artery immediately after induction of general anesthesia for monitoring of arterial pressure (AP) and for blood sampling for plasma norepinephrine (NE) and epinephrine (E) assay. After more than 30 min elapsed following induction of anesthesia and stable ET_{ISO} of 1.3 % was obtained for 15 min, the inspired concentration of isoflurane was increased to 5%, with the goal being to produce an ET_{ISO} of 2.6 % by adjusting the vaporizer (Drager Vapor 19.1 ; North American Drager, Telford, PA, U.S.A.) setting. AP and heart rate (HR) values were recorded every minute for 10 min, and measurements of plasma NE and E levels were made at baseline and at 1, 2, 3, 5, and 10 min after ET_{ISO} of 2.6 %. Arterial blood gas tensions and arterial pH (178 pH/Blood Gas Analyzer™, Corning, Medfield, MA, U.S.A.), plasma sodium, potassium and ionized calcium concentrations (NOVA 6™, NOVA biomedical, Waltham, MA, U.S.A.) were measured before and at 10 min after ET_{ISO} of 2.6%.

Blood samples were collected into heparinized tubes for analyses of arterial blood gases and plasma electrolytes concentrations, and into tubes containing sodium EDTA for analysis of plasma catecholamine concentrations. Plasma for catecholamine assays was quickly separated by centrifugation and stored frozen at −40 ℃ until assayed in a week. Concentrations of plasma catecholamines were analyzed by a high-performance liquid chromatography assay using diphenylethylenediamine as a fluorogenic reagent. Intra- and interassay coefficients of variation for NE and E were 0.95 % and 1.50 %, and 0.44 % and 1.30 %, respectively. The detection limit of both NE and E was 5 pg/ml.

Results were reported as means ± SEM. Statistical comparisons between groups were performed using two-way analysis of variance (ANOVA) followed by Student's t test. Changes in AP, HR and plasma catecholamine values over time were analyzed by repeated-measures ANOVA followed by Student's t test with Bonferroni correction for within group multiple comparisons. Testing for the incidence between groups was accomplished by a chi-squared analysis. A P value < 0.05 was considered significant.

Results

Two patients of the clonidine group and one patient of the control group were treated during the period of data collection, since systolic AP decreased below 70 mmHg in these patients within 1-4 min following ET_{ISO} of 2.6% (not significant in the incidence hypotension between groups). For these patients, only data obtained before hypotensive episodes were adopted for subsequent analyses.

There were no significant differences between the two groups in preanesthetic demographic data, doses of anesthetic agents for induction, and infusion rate of lactated Ringer's solution (Table 1). The clonidine dose administered was 4.96 μg/kg (4.68−5.26 μg/kg). Baseline systolic and diastolic APs, and plasma catecholamine concentrations (before the challenge with high isoflurane concentration) were lower in the clonidine group compared with the control group ($P < 0.05$, Table 2), but arterial blood gas and plasma electrolytes values did not differ between groups throughout the study.

Table 1 Patient characteristics, doses of anesthetic agents, and infusion rate of crystalloid solution

	Clonidine group (n=12)	Control group (n=13)
Clonidine (μg/kg)	4.94±0.06	0
Sex (M/F)	4/8	7/6
Age (year)	33±3	34±3
Height (cm)	163±3	164±3
Weight (kg)	56±4	56±3
Thiamylal (mg/kg)	4.86±0.03	4.87±0.04
Vecuronium (mg/kg)	0.204±0.003	0.203±0.002
LR ($ml \cdot kg^{-1} \cdot h^{-1}$)	22.8±1.5	22.0±1.1

Values are mean ± SEM.
LR = infusion rate of lactated Ringer's solution.

Following rapid increase in isoflurane concentration, significant elevations from baseline values were noted in systolic AP at 2-min recording and in diastolic AP at 1- and 2-min recordings ($P<0.05$), respectively in the control group, whereas in the clonidine group no significant transient AP increases were observed. However, there was only a significant difference between groups in diastolic AP changes from baselines at 1 min after ET_{ISO} of 2.6% (Fig. 1). Soon afterwards, systolic and diastolic APs returned to baselines, then decreased below baseline values during the remainder of study. Although HR increased significantly above baseline values from 2 to 7 min and from 1 to 6 min after the high isoflurane challenge in the clonidine and control groups, respectively ($P<0.05$), the magnitudes of HR increases were similar between groups (Fig. 1).

Plasma NE concentration remained less in the clonidine group compared with the control group during the entire study period ($P<0.05$). Following ET_{ISO} of 2.6%, plasma NE concentration increased in all patients of both groups, but the magnitudes of plasma NE elevations were similar between groups (Fig. 2). Because increases in plasma E concentrations following ET_{ISO} of 2.6% were not consistently found in all patients of both groups, significant changes from baseline values were noted in the clonidine group only at 2 and 3 min, and in the control group at 3 and 5 min after ET_{ISO} of 2.6%, respectively. However, no difference was found at any observation points between groups in changes of plasma E concentration. Arterial blood gas and plasma electrolytes values also remained unchanged and were similar between groups after exposure of the high isoflurane concentration.

Following abrupt increase in isoflurane concentration, none of the patients developed arrhythmias or arterial desaturation (oxygen saturation below

Table 2 Baseline hemodynamics, plasma catecholamine concentrations, and arterial blood gases before exposure of high isoflurane concentration

	Clonidine group (n =12)	Control group (n =13)
Systolic AP (mmHg)	88±2*	97±2
Diastolic AP (mmHg)	48±2*	56±2
HR (beats/min)	75±3	78±4
Norepinephrine (pg/ml)	159±20*	260±37
Epinephrine (pg/ml)	7±1*	18±3
pHa	7.52±0.01	7.50±0.01
Pa_{CO_2} (mmHg)	30±1	30±1
Pa_{O_2} (mmHg)	153±8	164±6

Values are mean ± SEM. AP = Arterial Pressure; HR = Heart Rate.
*$P<0.05$ *versus* control group.

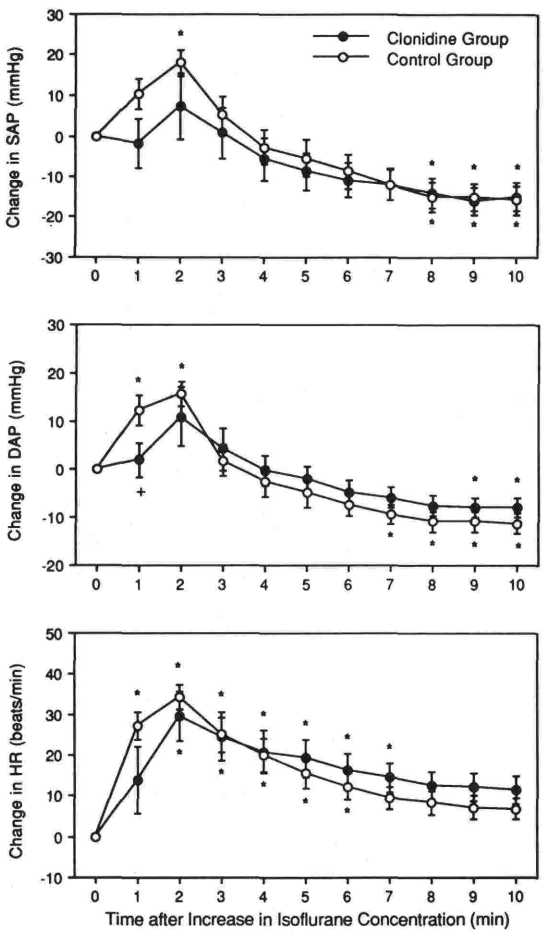

Figure 1 Changes (±SEM) in systolic arterial pressure (SAP), diastolic arterial pressure (DAP), and heart rate (HR) from baseline values after end-tidal isoflurane concentration was rapidly increased from 1.3% to 2.6%. *$P<0.05$ *versus* baseline. +$P<0.05$ *versus* control group.

95%). There were no other adverse reactions related to clonidine or high isoflurane concentration or interaction between the two agents.

Discussion

The results from the current study show that clonidine in a dose of 5 μg/kg as an oral preanesthetic medication is partially effective for attenuating the transient pressor response, but does not blunt elevations in HR and plasma catecholamine levels following rapid increase in isoflurane concentration. This partial suppressive effect of clonidine on the pressor response to an abrupt increase in isoflurane concentration indicates that isoflurane's sympathetic stimulation is more powerful so that clinical dose of oral clonidine medication cannot completely suppress these hemodynamic and catecholamine responses.

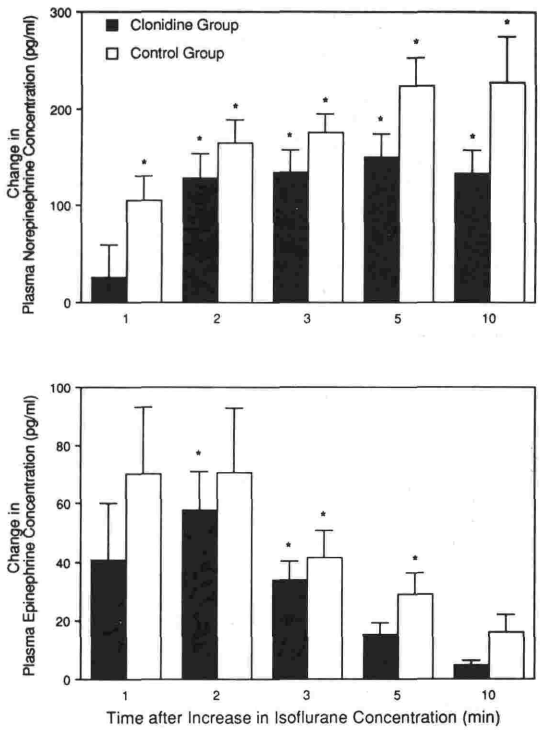

Figure 2 Changes (±SEM) in plasma norepinephrine and epinephrine concentrations from baseline values after end-tidal isoflurane concentration was rapidly increased from 1.3% to 2.6%. *$P < 0.05$ *versus* baseline.

According to previous clinical reports, cardiovascular stimulation associated with anesthetic and surgical stress was blunted by preanesthetic oral clonidine medication[8~11], and one of the most plausible underlying mechanisms is suppression of plasma catecholamine levels by clonidine medication[10]. Despite the limitations of plasma catecholamine levels as an index of overall sympathetic activity, lower plasma catecholamine concentrations seem to indicate attenuation of sympathetic hyperactivity[10]. Although in our results sustained significant reduction of plasma NE level was noted in patients receiving clonidine, the attenuating effect of clonidine medication on the hypertensive response was partial, and catecholamine release from the sympathetic nerves in response to a rapid increase in isoflurane concentration seemed not to have been essentially altered by preanesthetic oral clonidine medication (Fig. 2). These results indicate that oral clonidine medication in a dose of 5 μg/kg seems inadequate for complete suppression of catecholamine release and cardiovascular stimulation associated with high isoflurane exposure. However, administration of clonidine more than 5 μg/kg would be hazardous because of frequent occurrences of hemodynamic complications[18].

Compared with Yli-Hankala et al's report[1], the overall hemodynamic and catecholamine responses to an abrupt increase in isoflurane concentration were fundamentally similar to our results, although there were minor quantitative differences that could be attributed to different induction agent for anesthesia ; propofol in their study *versus* thiamylal in our study. Because of rapid recovery from propofol anesthesia[19], its action is likely to have remained to a lesser extent during high isoflurane challenge as compared to thiamylal. Indeed, complete data collection could not be accomplished in two patients in the clonidine group and one patient in the control group in this study, due to occurrences of profound hypotension. The failure of high isoflurane exposure to elicit any cardiovascular stimulation in these patients may be partly attributed to a decrease in sympathetic outflow by thiamylal

used for induction agent in our study[20]. Finally, our results are not entirely in agreement with more recent studies showing inhibitory effect of oral clonidine medication 3-4.3 μg/kg on cardiovascular stimulation and catecholamine responses elicited by isoflurane or desflurane[21,22]. These divergent results could be ascribed to differences in method of increasing isoflurane concentration (abrupt *versus* stepwise), administration route of isoflurane (*via* endotracheal tube *versus* mask), dose of oral clonidine (larger in our study than the other two studies), or different volatile anesthetics.

In summary, the current results showed that oral preanesthetic medication of clonidine 5 μg/kg medication partially attenuates the pressor response but does not blunt the HR and catecholamine responses to a rapid increase in isoflurane concentration in humans.

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