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Diuretic Effect of Clonidine during Isoflurane, Nitrous Oxide, and Oxygen Anesthesia

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Background: **Because clonidine, a relative selective α_2-agonist, inhibits the action of arginine vasopressin (AVP), the authors examined whether clonidine as an oral preanesthetic medication would induce diuresis and also would affect AVP release and its action during general anesthesia.**

Methods: **Fifty-seven patients (aged 18–65 yr) randomly received oral clonidine either approximately 5 $\mu g \cdot kg^{-1}$ (n = 19), approximately 2.5 $\mu g \cdot kg^{-1}$ (n = 19), or none (n = 19) in addition to oral famotidine 20 mg, 90 min before arrival at operating room. Urine volume, urine osmolality, and amount of sodium and potassium excreted into urine were examined every hour for 3 h during minor surgery under general anesthesia with isoflurane and nitrous oxide in oxygen. For 5 patients of each group, plasma AVP and atrial natriuretic peptide concentrations and urine cyclic adenosine monophosphate concentrations as an index of AVP action were also assayed.**

Results: **Urine output indices (calculated as hourly urine output [milliliters per hour] divided by body weight [kilograms]) were significantly greater in the all periods ($P \leq 0.035$) after the initiation of anesthesia in the patients receiving clonidine 5 $\mu g \cdot kg^{-1}$ and only in the 3rd h in those receiving clonidine 2.5 $\mu g \cdot kg^{-1}$ ($P = 0.047$) as compared with those in the patients given famotidine alone. The peak effects of diuresis and natriuresis induced by oral clonidine 5 $\mu g \cdot kg^{-1}$ were both observed at the 2nd h (mean ± SEM, 2.4 ± 0.4 $ml \cdot kg^{-1} \cdot h^{-1}$ and 5.7 ± 1.5 $mEq \cdot h^{-1}$ *vs.* 0.6 ± 0.1 $ml \cdot kg^{-1} \cdot h^{-1}$ and 2.2 ± 0.5 $mEq \cdot h^{-1}$ in the control subjects; $P = 0.001$ and $P = 0.049$). Kaliuresis also increased in the patients receiving clonidine 5 $\mu g \cdot kg^{-1}$ in the 2nd and 3rd h ($P \leq 0.003$). Urine osmolality showed a significant reduction over time in patients given clonidine but not in the control subjects. However, plasma AVP and atrial natriuretic peptide levels, and urine cyclic adenosine monophosphate concentrations did not significantly differ among the three groups.**

Conclusions: **Oral preanesthetic medication of clonidine 2.5 or 5 $\mu g \cdot kg^{-1}$ caused a significant diuretic effect during surgery under general anesthesia, though it did not apparently relate to AVP action. This effect of clonidine could be related to its pharmacological action as an α_2-adrenoceptor agonist not necessarily restricted to the kidney. The diuretic effect of clonidine implicates its clinical importance in the management of patients during anesthesia. (Key words: Anesthetics, gases: nitrous oxide. Anesthetics, volatile: isoflurane. Anesthetic techniques: general. Kidney: arginine vasopressin; clonidine; diuresis. Premedication, oral: clonidine. Sympathetic nervous system, α_2-adrenergic agonists: clonidine.)**

NUMEROUS previous clinical reports indicate that systemic as well as regional administration of clonidine, a preferential α_2-adrenergic agonist, has perioperative effects which include a reduction of anesthetic requirements,[1] improving hemodynamic stability,[2–4] and providing analgesia.[5] Likewise, clonidine alters the response to ephedrine and atropine in clinical dose,[6,7] and attenuates the sympathoadrenal responses.[8] Although action mechanisms of clonidine and its anesthesiologic importance have recently been extensively reviewed,[9] its clinical usefulness has not yet been completely defined.

Experimental evidence indicates that α_2-adrenoceptor agonists could inhibit the action of arginine vasopressin (AVP) on the renal collecting tubules[10–13] and that clonidine diminishes central vasopressin secretion[14,15] as well. Although conflicting results of clinical studies as to the effects of α_2-adrenoceptor agonists on plasma concentrations of AVP have been reported,[16–18] there are no data available describing whether preoperative administration of clonidine induces diuresis in anesthetized patients undergoing surgery. Because most anesthetic agents[19–21] and epidural[22,23] or spinal[24] anesthesia may impair renal hemodynamics and decrease urine output, a diuretic effect of clonidine, if any, could be of clinical importance.

Therefore, the goal of the current study is to assess whether clonidine would induce clinically significant

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diuresis in patients undergoing surgical interventions under general anesthesia, and further, to evaluate the influence of clonidine on both AVP secretion and the renal effect of AVP. Because a 5-$\mu g \cdot kg^{-1}$ dose of clonidine is most commonly used for preanesthetic medication,[9,25] we chose this dose for one of the three groups in the current study. Although our previous study[7] showed that only a larger dose (5 $\mu g \cdot kg^{-1}$) of clonidine blunts the heart rate response to intravenous atropine, we examined if clonidine 2.5 $\mu g \cdot kg^{-1}$ also would have a diuretic effect.

Materials and Methods

Fifty-seven adult ASA physical status 1 or 2 patients gave their informed consent to participate in research approved by Human Investigation Committee at the Gifu University Hospital and the University of Tsukuba Hospital. The subjects scheduled for elective surgery in the morning for otorhinolaryngologic or orthopedic procedures were included. Patients with a history of diabetes insipidus, diabetes mellitus, serum electrolyte abnormalities, anemia, renal dysfunction, hypertension, sinus bradycardia (heart rate < 60 beats $\cdot$ min^{-1}), and obesity exceeding standard body weight by 20% or more, were excluded from this study.

Each patient was randomly assigned to one of three groups. Subjects fasted for 8 h before the operation, and no intravenous fluid was administered until subjects arrived at operating room. The patients received either oral clonidine 2.5 $\mu g \cdot kg^{-1}$ (clonidine-2.5 group, n = 19), 5 $\mu g \cdot kg^{-1}$ (clonidine-5 group, n = 19) or none (control group, n = 19), in addition to oral famotidine 20 mg 90 min before arrival in operating room. Because in Japan clonidine is available only in 75- or 150-μg tablets (Catapres, Boehringer Ingelheim & Tanabe, Kawanishi City, Hyogo, Japan), 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 and observation during anesthesia were performed by the same anesthesiologist who was in charge of each anesthetic case.

The electrocardiogram (by electrocardiography), blood pressure (by sphygmomanometry), and hemoglobin oxygen saturation (by pulse oximetry) were monitored, and a 16-G intravenous cannula was placed into the forearm cutaneous vein. Lactated Ringer's solution was thereafter infused at a rate of 5 ml $\cdot$ $kg^{-1} \cdot h^{-1}$ until the end of anesthesia. General anesthesia was induced with intravenous thiamylal 4–5 mg $\cdot$ kg^{-1}, and tracheal intubation was facilitated with intravenous vecuronium 0.2 mg $\cdot$ kg^{-1}. Anesthesia was maintained by inhalation of 0.5–2.0% inspired isoflurane and 67% nitrous oxide in oxygen with 6 l $\cdot$ min^{-1} of the background gas flow. The lungs were mechanically ventilated to control arterial blood carbon dioxide tension between 35 and 40 mmHg. Each patient's blood pressure was kept within ±20% of the preoperative value by regulating the concentration of isoflurane. When blood pressure decreased to less than 80% of the preoperative value or heart rate decreased to less than 50 beats $\cdot$ min^{-1}, intravenous ephedrine 0.1 mg $\cdot$ kg^{-1} or atropine 0.01 mg $\cdot$ kg^{-1}, respectively, was administered.

An arterial cannula and a urinary catheter were placed in the radial artery and in the bladder, respectively, immediately after induction of general anesthesia. Urine was collected thereafter during anesthesia and surgery to gauge urine output immediately after the induction of anesthesia, and then every 60 min. Urine and blood samples were obtained simultaneously at the time of urine output measurement to measure urine and plasma electrolyte concentrations and osmolality, arterial blood gas tensions, *p*H, and HCO_3^-.

In 5 patients from each group we measured plasma concentrations of AVP and atrial natriuretic peptide (ANP) 1 day before surgery and every 60 min during anesthesia. Also, urine samples for an assay of cyclic adenosine monophosphate (AMP) were collected at every 60 min during anesthesia for those 15 subjects. The proposed surgery was started approximately 20 min after induction of anesthesia. This study was continued until 3 h after induction of anesthesia and no further collection of data was performed, because most of the surgical procedures were accomplished within 4 h after induction of anesthesia. Surgical interventions included intranasal polypectomy, radical antrostomy, sialoadenectomy, partial thyroidectomy, and arthrotomy of the extremities. Blood losses during surgery were within 100 ml. No additional intravenous fluid rather than lactated Ringer's solution (5 ml $\cdot$ $kg^{-1} \cdot h^{-1}$) were administered.

Blood samples were collected into heparinized tubes for analyses of osmolality and AVP and into tubes containing sodium ethylenediaminetetraacetic acid and aprotinin for analysis of ANP. Plasma was quickly separated by centrifugation and stored frozen at −40°C until assayed in 1 week. Urine samples for cyclic AMP assay were collected into tubes and also stored frozen at −40°C. Plasma and urine electrolyte concentrations,

plasma and urine osmolality, and blood gas tensions were determined with a multichannel electrolyte analyzer (NOVA 6, Nova, MA), a freezing-point depression analyzer (Osmometer OM801, Vogel, Germany), and *p*H–blood gas analyzer (178, Corning, Medfield, MA), respectively. Isoflurane concentrations were determined from readings of dial of vaporizer (Drager Vapor 19.1, North American Drager, Telford, PA) and plotted as time–concentration line chart. Concentrations of plasma AVP, plasma ANP, and urine cyclic AMP were analyzed using radioimmunoassay kits (Mitsubishi Petrochemical, Tokyo, Japan; Shionogi, Osaka, Japan; Yamasa, Tokyo, Japan, respectively) and a γ-scintillation counter (ARC950, Aroka, Tokyo, Japan). Intra- and interassay coefficients of variation for AVP, ANP, and cyclic AMP were 6.2% and 9.1%, 4.5% and 5.1%, and 2.4% and 1.6%, respectively.

Results are reported as means ± SEM. Urine output index (milliliters per kilogram per hour), free water clearance (milliliters per minute), and fractional excretion of electrolytes (milliliters per hour) were calculated as follows:

$$\text{Urine output index} = \frac{\dot{U}}{BW}$$

$$\text{Free water clearance} = \frac{\dot{U}}{60} - \frac{\dot{U} \cdot U_{osm}}{60 \cdot P_{osm}}$$

$$\text{Fractional excretion of electrolytes} = \frac{\dot{U} \cdot U_{elec}}{P_{elec}}$$

where $\dot{U}$ = urine output (milliliters per hour); BW = body weight (kilograms); U_{osm} = urine osmolality (milliosmoles per kilogram); P_{osm} = plasma osmolality (milliosmoles per kilogram); U_{elec} = urinary electrolyte concentration (milliequivalents per liter); and P_{elec} = plasma electrolyte concentration (milliequivalents per liter). One-way analysis of variance was used for comparisons of subject characteristic variables among groups. For comparisons of variables during anesthesia and laboratory data, one-way analysis of variance for repeated measurements with three grouping factors was used. Tukey's HSD (honestly significant difference) test was used for further multiple comparisons between groups and paired Student's *t* test with Bonferroni correction was used for intragroup multiple comparisons. Testing for the incidence between groups, such as number of ephedrine administrations, was accomplished by a chi-squared analysis. Isoflurane concentrations were expressed as the mean time averaged concentrations. They were obtained by calculating the sum of the areas determined by the time–concentration plot derived from the readings of the dial of vaporizer and were normalized by 180 min (*i.e.*, the time from induction of anesthesia to the end point of the study). Then one-way analysis of variance and Tukey's HSD test were applied to comparisons of the three groups. A P value < 0.05 was considered significant for all of the statistic tests.

Results

There were no significant differences among the three groups in preanesthetic demographic data, plasma electrolyte concentrations, blood urea nitrogen level, and serum creatinine concentration (table 1). Clonidine doses administered were 2.60 ± 0.05 $\mu g \cdot kg^{-1}$ for the clonidine-2.5 group, and 4.93 ± 0.07 $\mu g \cdot kg^{-1}$ for the clonidine-5 group. The volume, sodium, potassium and osmolality of urine measured and discarded at the beginning of anesthesia did not differ significantly among the three groups (table 2). Normalized mean isoflurane concentrations in the clonidine-2.5 group (0.83 ± 0.06%) and the clonidine-5 group (0.76 ± 0.08%) were significantly less as compared with the control group (1.10 ± 0.07%) (table 2).

The patients receiving clonidine 5 $\mu g \cdot kg^{-1}$ had larger amounts of urine output than did the patients in other two groups. Urine output in all hourly periods was significantly greater in the clonidine-5 group, from induction to 1 h (1.57 ± 0.40 in the clonidine-5 group *vs.* 0.62 ± 0.11 $ml \cdot kg^{-1} \cdot h^{-1}$ in the clonidine-2.5 group [$P = 0.022$] or *vs.* 0.68 ± 0.09 $ml \cdot kg^{-1} \cdot h^{-1}$ in the control group [$P = 0.035$]), from 1 to 2 h (2.37 ± 0.40 *vs.* 0.63 ± 0.09 $ml \cdot kg^{-1} \cdot h^{-1}$ in the control group

Table 1. Patient Characteristics of Three Groups

	Control Group	Clonidine-2.5 Group	Clonidine-5 Group
Clonidine (μg/kg)	0	2.60 ± 0.05	4.93 ± 0.07
No. of patients	19	19	19
Sex (M/F)	9/10	9/10	10/9
Age (yr)	38 ± 4	39 ± 4	38 ± 3
Height (cm)	161 ± 3	160 ± 2	163 ± 2
Weight (kg)	56 ± 3	56 ± 3	57 ± 2
BUN (mg/dl)	12.2 ± 0.8	11.4 ± 0.6	13.2 ± 0.9
Cre (mg/dl)	0.7 ± 0.03	0.8 ± 0.04	0.8 ± 0.07

Values are mean ± SEM.

BUN = blood urea nitrogen; Cre = serum creatinine concentration.

Table 2. Urine Volume, Urine Osmolality, Urine Sodium, and Potassium at the Beginning of Anesthesia, and Normalized Isoflurane Concentration during Anesthesia

	Control Group	Clonidine-2.5 Group	Clonidine-5 Group
Volume (ml)	66.8 ± 13.8	32.9 ± 9.8	58.0 ± 15.3
Osmolality (mOsm/kg)	694 ± 47	806 ± 30	712 ± 51
Sodium (mEq/L)	10.2 ± 2.0	5.3 ± 1.8	6.2 ± 1.3
Potassium (mEq/L)	3.3 ± 0.7	2.1 ± 0.4	2.6 ± 0.8
Isoflurane (%)	1.1 ± 0.07	0.8 ± 0.06*	0.8 ± 0.08*

Values are mean ± SEM.

* $P < 0.05$ *versus* the control group.

[$P = 0.001$]), and from 2 to 3 h (1.90 ± 0.33 *vs.* 0.45 ± 0.09 ml · kg^{-1} · h^{-1} in the control group [$P = 0.004$]) after the induction of general anesthesia (fig. 1). In the clonidine-2.5 group, urine output index was significantly greater only in the 3rd h than the control group. Although urine osmolality during the 1st h in the clonidine-2.5 group was significantly greater as compared with the control group ($P = 0.012$), it decreased significantly during the subsequent two periods in both clonidine groups, and there were no significant differences among the three groups (fig. 2).

Free water clearance did not differ among the three groups, although in the clonidine-5 group it significantly increased during the 2nd and 3rd h ($P \leq 0.05$) as compared with that during the 1st h (table 3). Both the urinary excretion of sodium and the fractional excretion of sodium in the 2nd h were significantly greater in the clonidine-5 group than the control group ($P \leq 0.049$, fig. 3), whereas both the urinary excretion of potassium and the fractional excretion of potassium during the 2nd and 3rd h in the clonidine-5 group were significantly greater than the control group ($P \leq 0.004$, fig. 3).

Concentrations of plasma AVP and ANP, and urinary cyclic AMP neither changed over time nor statistically differed among the three groups (fig. 4).

Baseline hemodynamic data were comparable among groups (table 4). There were no differences in mean blood pressure at any time among groups, although the mean values of heart rate at induction of anesthesia in the clonidine-5 group and at the last measurement in the clonidine-2.5 group were significantly less as compared with the control group. Four patients in the clonidine-5 group, one patient in the clonidine-2.5 group and four patients in the control group received ephedrine, whereas five patients in the clonidine-5 group, one patient in the clonidine-2.5 group, and two patients in the control group received atropine for the treatment of hypotension and bradycardia, respectively. All of the patients responded well to these treatments. The incidence of either ephedrine or atropine administration was not significantly different among the three groups.

Mean values of arterial blood gas tensions, *p*H, bicarbonate concentrations and base excess were similar among groups (table 5). Plasma osmolality was significantly higher in the clonidine-2.5 group than in the other two groups during anesthesia, although no significant differences were noted in blood glucose levels or plasma sodium and potassium concentrations among the three groups (table 6).

Discussion

The results from the current study demonstrate that clonidine in a dose of 2.5 or 5 $\mu g \cdot kg^{-1}$ as an oral preanesthetic medication significantly increased urine output and urinary sodium and potassium excretion. This effect of clonidine appears neither to be mediated primarily by its influence on AVP release, its modulation of the AVP action on the function of renal collecting

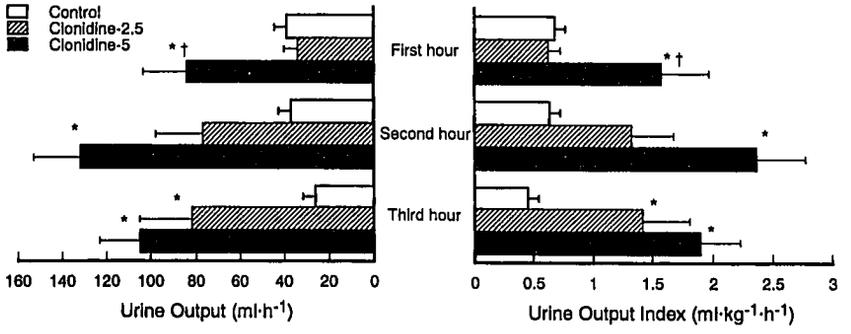

Fig. 1. Urine output and urine output index during anesthesia. First-hour period = from induction of general anesthesia to 1 h after induction; 2nd-h period = from 1 to 2 h after induction; 3rd-h period = from 2 to 3 h after induction. *$P < 0.05$ *versus* control group; †$P < 0.05$ *versus* clonidine-2.5 group.

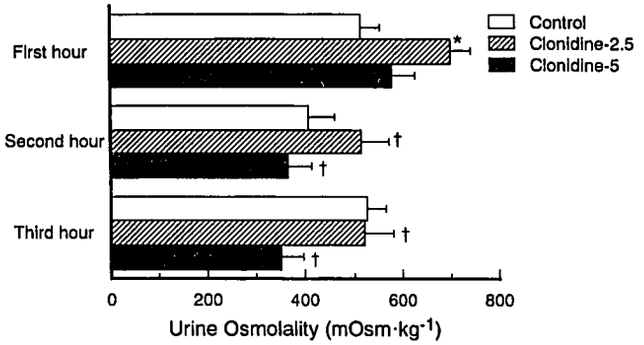

Fig. 2. Urine osmolality during anesthesia. First-hour period = from induction of general anesthesia to 1 h after induction; 2nd-h period = from 1 to 2 h after induction; 3rd-h period = from 2 to 3 h after induction. *$P < 0.05$ *versus* control group; †$P < 0.05$ *versus* 1st h.

tubules, nor on enhancing ANP release. Although the mechanism of clonidine-induced diuresis seems to be different from one observed in previous animal experiments,[12,13] the current results are the first observation showing that clonidine's diuretic effect is evident in humans undergoing anesthesia and surgical stimulation.

Several mechanisms for diuretic effect of α_2-agonists have been proposed. A carefully designed experiment in rat by Gellai and Edwards[12] has shown that an α_2-agonist directly inhibits AVP action on renal collecting tubules and causes diuresis with an evidence of significant reduction in AVP-stimulated cyclic AMP accumulation. In this mechanism of clonidine action, however, there seems to be a marked inter-species difference in the ability of α_2-adrenoceptor agonists to inhibit AVP induced cyclic AMP accumulation at the renal tubular level as shown in their subsequent *in vitro* study.[26] Other possible mechanisms of diuresis by α_2-agonists include decreased central AVP secretion,[14,15] and inhibition of renal sympathetic nerve activity.[27,28] There are recent reports that AVP levels in both plasma[17,18] and cerebrospinal fluid[17] decreased after administration of clonidine 5 $\mu g \cdot kg^{-1}$ orally[17] or 0.7–2.1 $\mu g \cdot kg^{-1}$ intravenously[18] in awake humans, although Pouttu *et al.*[29] reported that clonidine 4.5 $\mu g \cdot kg^{-1}$

Table 3. Hourly Free Water Clearance (ml/min) during Anesthesia

	Control Group	Clonidine-2.5 Group	Clonidine-5 Group
First hour period	−0.38 ± 0.09	−0.63 ± 0.13	−1.00 ± 0.28
Second hour period	−0.10 ± 0.11	−0.08 ± 0.40	0.12 ± 0.35*
Third hour period	−0.33 ± 0.10	−0.26 ± 0.52	0.22 ± 0.31*

Values are mean ± SEM.

First hour period = a period from the induction of general anesthesia to 1 h after the induction; Second hour period = a period from 1 h to 2 h after the induction; Third hour period = a period from 2 h to 3 h after the induction.

* $P < 0.05$ *versus* First hour period.

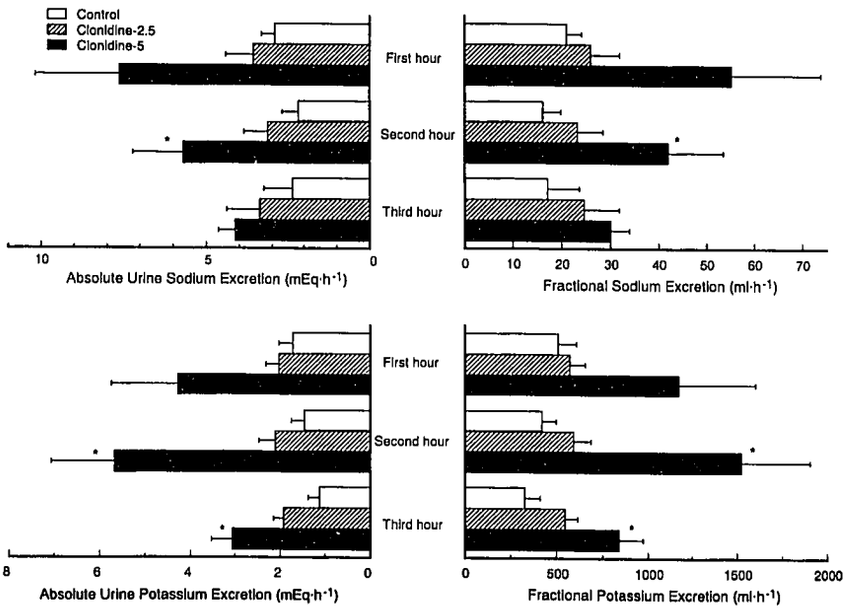

Fig. 3. Absolute and fractional urinary excretion of sodium and potassium during anesthesia. First-hour period = from induction of general anesthesia to 1 h after induction; 2nd-h period = from 1 to 2 h after induction; 3rd-h period = from 2 to 3 h after induction. *$P < 0.05$ *versus* control group.

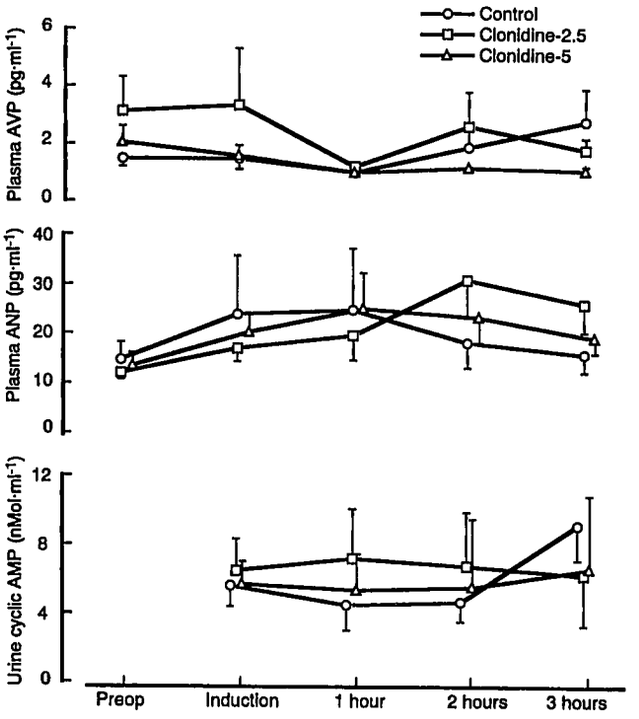

Fig. 4. Concentrations of plasma arginine vasopressin (AVP), atrial natriuretic peptide (ANP), and urinary cyclic adenosine monophosphate (AMP). Preop = 1 day before surgery; Induction = at induction of anesthesia; 1 h = at 1 h after induction; 2 h = at 2 h after induction; 3 h = at 3 h after induction.

orally failed to decrease plasma AVP level during and after surgery under general anesthesia. However, they did not show any data on urine output. Because plasma AVP and urinary cyclic AMP levels as an index of AVP action did not differ among the three groups of patients in the current results (fig. 4), these mechanisms of clonidine's diuretic action seems unlikely to be involved in anesthetized humans undergoing surgery. Another proposed mechanism independent from AVP activity is that clonidine may cause diuresis by releasing ANP,[30] the diuretic effect of which may be in turn enhanced by clonidine.[31] However, because plasma ANP concentration did not show significant differences among groups in the current study (fig. 4), we could not confirm if there were any correlations among clonidine, ANP and diuresis.

There are many factors affecting urine output during anesthesia and surgery; these include renal blood flow (RBF), glomerular filtration rate, blood volume, plasma osmolality, activities of the autonomic nervous and endocrine systems,[32] and presumably hypo- or hypercapnia, acidosis, plasma electrolyte balance, altered intrathoracic pressure due to mechanical ventilation, differences in anesthetic agents, and systemic hemodynamics as well. Any of these may modulate clonidine-induced diuresis. In the current study these factors, except for blood pressure, were either absent or similarly present. Indeed, significant reductions in mean blood pressure below the baseline values were noted after general anesthesia induction in all groups, and they persisted during the remainder of study period in patients given clonidine (table 4). However, significant differences in mean blood pressure did not exist among the three groups, and if lower blood pressure did affect the results, lower blood pressure might have rather contributed to decrease urine output through baroregulatory mechanisms to stimulate AVP secretion.[33] But it is unlikely in the current study, because plasma AVP concentrations did not increase in the clonidine groups and were not different among the three groups (fig. 4). Oral clonidine 300 μg in awake humans[8] or oral premedication with clonidine 5 $\mu g \cdot kg^{-1}$ in anesthetized humans[2] seems not to reduce cardiac output, and in the current study mean blood pressure during anesthesia and surgery in patients given clonidine was within the range of autoregulation of RBF.[32] In addition, acute deliberate hypotension by clonidine did not re-

Table 4. Mean Blood Pressure and Heart Rate

	Control Group	Clonidine-2.5 Group	Clonidine-5 Group
Mean blood pressure (mmHg)			
Baseline	85 ± 2.3	89 ± 2.3	85 ± 2.1
Induction	75 ± 2.1*	75 ± 2.2*	73 ± 1.3*
1 h	82 ± 2.5	81 ± 2.1*	78 ± 1.4*
2 h	84 ± 2.4	77 ± 2.4*	82 ± 1.9
3 h	83 ± 2.6	79 ± 2.4*	80 ± 1.7*
Heart rate (beats/min)			
Baseline	70 ± 1.6	70 ± 2.4	73 ± 1.6
Induction	70 ± 2.2	70 ± 2.9	62 ± 1.7*†‡
1 h	77 ± 3.6	69 ± 2.5	69 ± 2.0
2 h	83 ± 4.0*	72 ± 2.9	73 ± 3.2
3 h	84 ± 4.1*	73 ± 2.3†	74 ± 2.7

Values are mean ± SEM.

Baseline = preanesthetic values at the wards; Induction = values at the induction of general anesthesia; 1 h = values at 1 h after the induction; 2 h = values at 2 h after the induction; 3 h = values at 3 h after the induction.

* $P < 0.05$ *versus* the baseline.

† $P < 0.05$ *versus* the control group.

‡ $P < 0.05$ *versus* the Clonidine-2.5 group.

Table 5. Arterial Blood Gases

	Control Group	Clonidine-2.5 Group	Clonidine-5 Group
*p*H			
Induction	7.45 ± 0.01	7.44 ± 0.01	7.44 ± 0.01
1 h	7.41 ± 0.01	7.43 ± 0.01	7.43 ± 0.01
2 h	7.41 ± 0.01	7.42 ± 0.01	7.40 ± 0.01
3 h	7.40 ± 0.01	7.41 ± 0.01	7.40 ± 0.01
Pa_{CO_2} (mmHg)			
Induction	33 ± 0	36 ± 1	34 ± 1
1 h	37 ± 1	37 ± 1	35 ± 1
2 h	37 ± 1	37 ± 1	37 ± 1
3 h	38 ± 1	37 ± 1	38 ± 1
Pa_{O_2} (mmHg)			
Induction	174 ± 9	176 ± 8	165 ± 6
1 h	165 ± 9	167 ± 5	164 ± 7
2 h	166 ± 7	168 ± 4	170 ± 6
3 h	164 ± 7	164 ± 4	165 ± 6
HCO_3- (mEq/L)			
Induction	23.1 ± 0.4	24.2 ± 0.5	23.1 ± 0.6
1 h	23.7 ± 0.3	24.4 ± 0.5	23.4 ± 0.5
2 h	23.5 ± 0.3	23.9 ± 0.4	23.2 ± 0.5
3 h	23.7 ± 0.3	23.8 ± 0.4	23.4 ± 0.6
BE (mEq/L)			
Induction	−0.2 ± 0.4	1.2 ± 0.4	−0.4 ± 0.7
1 h	−0.3 ± 0.4	1.0 ± 0.4	−0.5 ± 0.7
2 h	−0.5 ± 0.3	0.4 ± 0.5	−0.9 ± 0.6
3 h	−0.3 ± 0.4	0.2 ± 0.4	−0.7 ± 0.7

Values are mean ± SEM.

Pa_{CO_2} = arterial blood carbon dioxide tension; Pa_{O_2} = arterial blood oxygen tension; HCO_3- = arterial blood bicarbonate concentration; BE = arterial blood base excess; Baseline = preanesthetic values at the wards; Induction = values at the induction of general anesthesia; 1 h = values at 1 h after the induction; 2 h = values at 2 h after the induction; 3 h = values at 3 h after the induction.

duce RBF in rats.[34] Conversely, isoflurane anesthesia reduced both RBF and glomerular filtration rate,[21] although cardiac output was well maintained at 0.9 to 1.9 minimum alveolar concentration (MAC) of isoflurane.[35] As reported previously,[1,36] the patients receiving preanesthetic clonidine medication needed a significantly lower concentration of isoflurane in the current study (table 2). Therefore, one can also assume that higher concentration of isoflurane in patient not given clonidine might have partly contributed to reductions in RBF and thus urine output, whereas lower concentration of isoflurane in patients given clonidine and clonidine *per se* might have maintained RBF and thus urine output.

Urine output could be influenced not only by plasma levels of AVP and other hormones such as catecholamines, but also by anesthetic depth of isoflurane which may in turn affect plasma levels of catecholamines.[37,38] Isoflurane has been shown not to affect plasma AVP concentration in the rabbit,[39] whereas a clinical report showed that 1.1% isoflurane with 65% nitrous oxide in oxygen (approximately 1.5 MAC as anesthetic gas mixture) decreased plasma AVP levels by approximately 50% of the control values (9.9 pg · ml^{-1}) before surgery.[40] However, the same concentration of isoflurane was unable to suppress AVP secretion as a stress response to major surgical procedures such as cholecystectomy, resulting in a fourfold increase in plasma AVP levels.[40] In the current study, the patients only had minor surgery in the ear, neck and throat, and plasma AVP levels remained essentially unchanged in relatively low range during the entire study period in

Table 6. Plasma Electrolytes and Blood Glucose Concentrations, and Plasma Osmolality

	Control Group	Clonidine-2.5 Group	Clonidine-5 Group
Plasma sodium concentration (mEq/L)			
Baseline	141 ± 0.5	140 ± 0.7	140 ± 0.6
Induction	139 ± 0.8*	137 ± 0.6*	138 ± 0.7*
1 h	137 ± 0.6*	136 ± 0.6*	137 ± 0.7
2 h	137 ± 0.6*	137 ± 0.6*	138 ± 0.8
3 h	137 ± 0.7*	135 ± 0.9*	137 ± 0.9
Plasma potassium concentration (mEq/L)			
Baseline	4.2 ± 0.1	4.1 ± 0.1	4.2 ± 0.1
Induction	3.5 ± 0.1*	3.5 ± 0.1*	3.7 ± 0.1*
1 h	3.5 ± 0.1*	3.5 ± 0.1*	3.7 ± 0.1*
2 h	3.5 ± 0.1*	3.5 ± 0.1*	3.7 ± 0.1*
3 h	3.6 ± 0.1*	3.6 ± 0.2*	3.7 ± 0.1*
Blood glucose concentration (mg/dl)			
Baseline	93 ± 4.4	85 ± 2.3	91 ± 9.6
Induction	114 ± 4.5*	116 ± 3.8*	116 ± 4.2*
1 h	117 ± 5.5*	116 ± 4.6*	116 ± 4.1*
2 h	123 ± 7.3*	116 ± 8.8*	121 ± 6.2*
3 h	128 ± 6.3*	123 ± 6.9*	124 ± 8.1*
Plasma osmolality (mOsm/kg)			
Baseline (n = 5)	284 ± 2.3	287 ± 1.9	287 ± 1.6
Induction	287 ± 1.3	292 ± 1.6†‡	285 ± 0.8
1 h	289 ± 1.3	292 ± 1.8‡	287 ± 1.0
2 h	289 ± 1.3	293 ± 1.6‡	288 ± 1.0
3 h	289 ± 1.1	293 ± 1.5‡	288 ± 1.0

Values are mean ± SEM.

Baseline = preanesthetic values at the wards; Induction = values at the induction of general anesthesia; 1 h = values at 1 h after the induction; 2 h = values at 2 h after the induction; 3 h = values at 3 h after the induction.

* $P < 0.05$ *versus* baseline.

† $P < 0.05$ *versus* the control group.

‡ $P < 0.05$ *versus* the Clonidine-5 group.

each group and were comparable among groups (fig. 4). Therefore, no significant alterations in the AVP levels presumably reflect that the surgical stimuli in our patients might have caused less stress and thus less humoral responses as compared with those in previous reports.[29,40]

Because the peak plasma concentration of clonidine is attained at 1 to 3 h following its oral administration,[41] it is possible that diuretic effects of clonidine could have started to be evident around that time. However, in the current study the diuretic effect of clonidine was not clinically obvious immediately after anesthesia induction, approximately 2 h after administration of clonidine (table 2). This may be ascribed in part to fluid restriction for 8 h before anesthesia. In the current study we only measured the urine output for 3 h during anesthesia because of brief surgical procedure, although the elimination half-life of clonidine is about 12 h, ranging from 6 to 24 h,[41] and diuretic effect of clonidine might be expected to persist into the postoperative period following minor surgery.

A decrease in urine flow during anesthesia and surgery is not necessarily of clinical importance in healthy individuals. On the other hand diuretics such as furosemide, mannitol, and dopamine may be used in patients undergoing more major surgery to counteract a significant decrease in urine output during anesthesia,[42] provided adequate circulatory volume is maintained. However, they sometimes cause plasma electrolyte imbalance—a decrease in plasma sodium and potassium concentrations. In the current study, the significant increases in urinary excretion of sodium and potassium in the patients given clonidine were not associated with any changes in plasma electrolytes and osmolality, though plasma osmolality remained higher in the clonidine-2.5 group during anesthesia. (table 6). Reasons for this are unclear. Because a change in plasma osmolality of 1% would be expected to alter plasma AVP levels by approximately 1 $pg \cdot ml^{-1}$,[43] it is possible that the increase in plasma osmolality might have antagonized, at least partially, the clonidine's diuretic effect in the clonidine-2.5 group. More likely, individual variabilities concerning preoperative condition as well as responses to drugs and stimuli during anesthesia and surgery might explain these current results. Among agents currently used for preanesthetic medications, there has been no description as to whether premedicants affect urine output during anesthesia. For example, although an anesthetic dose of morphine causes urine output to decrease in rats[44] or dogs[45] presumably through increasing AVP release, its use as preanesthetic medication does not seem to affect urine output in humans during anesthesia,[46] and no data are available for other premedicants in this regard. Thus, clonidine as a premedicant may *via* its diuretic action be of clinical importance for patient care during anesthesia.

In conclusion, the current study showed that clonidine as an oral premedicant has diuretic and natriuretic effects in humans under general anesthesia during surgical procedures. The underlying mechanism(s) for these effects of clonidine seems different than that described in animal experiments, as inhibition of AVP-stimulated cyclic AMP accumulation in renal collecting tubules. To clarify the principal mechanisms of clonidine's diuretic action in patients, a further study is needed to measure RBF and glomerular filtration rate in humans without anesthesia and surgery.

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