Renal Effects of Medetomidine in Isoflurane-Anesthetized Dogs with Special Reference to Its Diuretic Action

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ABSTRACT. Renal effects of the selective α₂-adrenoceptor agonist, medetomidine, were investigated in anesthetized dogs. Animals were administered medetomidine 20 and 40 µg/kg intravenously (IV) and 80 µg/kg intramuscularly (IM) or 1 ml of saline IV. Urine and blood samples were collected before and at 30, 60, 90 and 120 min following medetomidine injection. Mean arterial blood pressure (MABP), renal blood flow (RBF), glomerular filtration rate (GFR), urine volume (Uv), urine osmolality (Uosm), free water clearance (C\text{H}_2\text{O})}, fractional clearance of sodium (\text{F}_Na), plasma osmolality (\text{Posm}), plasma glucose levels and plasma antidiuretic hormone (ADH) concentrations were measured. The results showed that IV administration of medetomidine initially increased MABP 5–15 min followed by long-lasting decrease. The initial hypertension was not observed after IM administration, which was accompanied by a more profound hypotensive effects. RBF, GFR, Uv, C\text{H}_2\text{O} increased after IV injection and decreased after IM. Medetomidine increased \text{F}_Na and \text{Posm} and decreased Uosm. Plasma glucose levels initially increased and subsequently decreased. Plasma ADH concentration was decreased by IV injection but increased by IM administration. Our data imply that: 1) IV administration of medetomidine at dose rates of 20 and 40 µg/kg results in profound diuresis up to 2 hr; 2) Suppression of ADH release from the CNS is one of the mechanisms of medetomidine-induced diuresis although it may not be the principal one.

KEY WORDS: anesthesia, canine, isoflurane, medetomidine and renal function.

The effects of anesthesia on renal functions may occur through direct action of some anesthetics that are nephrotoxic or indirectly through the effects on hemodynamic or neuroendocrine responses with relatively non-toxic drugs [21, 22]. The observed major effects of anesthesia on renal functions have been reported to be due to indirect circulatory and neuroendocrine responses [4, 12]. Alpha₂-adrenoceptor agonists have been shown to have many advantages desired in anesthetic, which include sedation, analgesia and muscle relaxation [14, 15, 26], however, previous studies have demonstrated the ability of these drugs to alter hemodynamic, initially they rise mean arterial blood pressure (MABP) due to their effects on postsynaptic α₂-adrenoceptors with the resultant increase in systemic vascular resistance [27], this is followed by long-lasting decrease due to stimulation of central and peripheral presynaptic α₂-adrenoceptors, therefore decrease sympathetic outflow and reduce cardiac output. These hemodynamic alterations can greatly affect the renal perfusion and result in consistent changes in renal functions [17, 25, 32]. On the other hand increased urine production after administration of α₂-adrenoceptor agonists has been reported for different animal species [5, 7, 23, 33]. The real cause of α₂-agonists-induced diuresis is still unclear. Possible mechanisms include, increasing RBF and GFR, inhibition of antidiuretic hormone (ADH) release from posterior pituitary [28, 31], interference with the hydrosmotic action of ADH on the collecting ducts [10, 11, 30], inhibiting the release of insulin with the resultant glucosuria and osmotic diuresis [20, 33]. Medetomidine is one of the almost recently introduced α₂-agonist approved for veterinary use and it has been proved to be a very potent highly specific α₂-agonist when compared to other α₂-agonist [9, 16]. The α₂-to-α₁ selectivity ratio for medetomidine is approximately ten times that of xylazine [9]. A little about renal effects of medetomidine in dogs has been documented. The aim of the present study was to clarify those renal effects of medetomidine in dogs with special reference to its diuretic action.

MATERIALS AND METHODS

Animals: Sixteen healthy (3 to 4 years old) laboratory male beagle dogs of mean weight 17 kg were used in this study. The animals were housed in approved facilities and fed a commercial food until the end of study. Dogs were determined to be healthy on the basis of physical examination, complete blood cell count and serum biochemical analysis, and each animal was studied after an overnight fast. The experiments were conducted according to the guidelines for the care and use of laboratory animals, Graduate School of Agriculture and Biological Sciences, Osaka Prefecture University.

Experimental protocol: On the day of experiment, the cephalic vein was catheterized with a 22 gauge over needle catheters which capped, secured in place with tape and flushed with heparinized 0.9% NaCl for injection of anes-
thetics and infusion of p-amino hippuric acid (PAH) (Nacalai Tesque Inc., Kyoto). Urinary catheters were inserted, secured and remained in place until the end of experiment. Anesthesia was induced by propofol 6 mg/kg intravenously (IV) and was maintained by isoflurane. After the initiation of anesthesia, PAH was given IV as a bolus by a priming dose of 6 mg/kg body weight over 5 min followed by constant IV infusion (0.3 mg/kg/min) at a rate of 2 ml/min in lactated Ringer’s solution during experiment [13, 19]. Equilibration period of 30 min was allowed after the initiation of PAH infusion. Blood samples were collected and the bladder was emptied by gentle aspiration to obtain baseline urine samples. Twenty min period of urine collection was performed. Mean arterial blood pressure (MABP) was measured indirectly by a cuff applied on the fore leg and monitored before and at 5, 10 min and then every 10 min after medetomidine administration until the end of the experiment. Five min after baseline sample collection, medetomidine (Meiji Seika Kaisha Ltd, Tokyo), 20 µg/kg IV (4 dogs), 40 µg/kg IV (4 dogs) and 80 µg/kg intramuscularly (IM) (4 dogs) or 1 ml saline solution IV (4 dogs) (control) was injected. Urine and blood samples were collected at 30, 60, 90 and 120 min after medetomidine or saline injection. Blood samples were placed in tubes containing sodium ethylenediamine tetra-acetic acid for separation of plasma, samples were placed into small heparinized tubes for measuring hematocrite values (HCT), another blood samples were placed into serum tubes, centrifuged and serum was separated within 1 hr after collection. Urine samples were centrifuged and plasma, serum and urine supernatant samples were stored at –30°C until assayed within 1–2 months.

**Analytical methods:** Plasma and urinary PAH concentrations were measured calorimetrically [3]. Plasma glucose and creatinine concentrations were measured by using automated analyzer (Cobasready, Nihon Roche Inc., Tokyo). Samples for plasma ADH, plasma osmolality (Posm), urine osmolality (Uosm), plasma and urine sodium concentrations and urine creatinine concentrations were analyzed by the Japan clinical laboratory (Osaka).

**Clearance studies:** Clearance values were determined using standard equations.

Creatinine clearance (C\textsubscript{\text{Cr}}) which is a marker for glomerular filtration rate (GFR) was calculated as: C\textsubscript{\text{Cr}} (ml/min/kg) = U\textsubscript{v}×U\textsubscript{c}/P\textsubscript{c}. Where U\textsubscript{v} is the urine volume, U\textsubscript{c} is the urine concentration of creatinine and P\textsubscript{c} is the plasma concentration of creatinine.

PAH clearance (CPAH) which is a marker for renal plasma flow (RPF), was calculated as: CPAH (ml/min/kg) = U\textsubscript{v}×U\textsubscript{PAH}/P\textsubscript{PAH}. Where U\textsubscript{v} is the urine volume, U\textsubscript{PAH} is the urine concentration of PAH and P\textsubscript{PAH} is the plasma concentration of PAH. Renal blood flow (RBF) was calculated from renal plasma flow and HCT as: RBF (ml/min/kg) = RPF × 100/100-HCT.

Fractional clearance of sodium (F\textsubscript{Na}) was calculated as: F\textsubscript{Na} (%) = UNa/PNa × P\textsubscript{Na}/U\textsubscript{Na} × 100. Where UNa is the urinary sodium concentration and P\textsubscript{Na} is the plasma concentration of sodium. This gives the clearance of sodium as a percentage of creatinine clearance.

Free water clearance (C\textsubscript{H2O}) was calculated as: C\textsubscript{H2O} (ml/min) = U\textsubscript{v}×U\textsubscript{osm}/P\textsubscript{osm}. Where U\textsubscript{v} is the urine volume, U\textsubscript{osm} is the urine osmolality and P\textsubscript{osm} is the plasma osmolality.

**Statistical analysis:** The data were subjected to statistical analysis using one-way analysis of variance followed by Fisher’s least significant difference test. Differences at \(p<0.05\) were considered significant.

**RESULTS**

**Mean arterial blood pressure:** Intravenous administration of medetomidine at 20 and 40 µg/kg showed biphasic changes on MABP, an initial increase lasted 5–15 min followed by a long-standing decrease below the pre-injection values. The hypertensive effect was significant after IV but not IM. Significant hypotension was seen in animals received 80 µg/kg IM (Fig. 1).

**Renal variables:** The effects of administration of different dose rates of medetomidine on renal variables are summarized in (Fig. 2). RBF increased after IV administration with significant differences from respective control values at 60 min for the 20 µg/kg dose and at 60, 90, 120 min for the 40 µg/kg dose. With IM administration of 80 µg/kg, RBF significantly decreased at 60, 90 and 120 min (Fig. 2a).

GFR increased by IV injection with significant differences from control values at 60, 90, 120 min for the 20 µg/kg medetomidine dose and at 30, 60, 90, 120 min for the 40 µg/kg dose. In animals given 80 µg/kg IM, GFR significantly decreased at 60, 90 and 120 min (Fig. 2b). Significant increase in U\textsubscript{v} was observed at 60, 90 and 120 min for both IV doses, while in animals treated with 80 µg/kg IM, U\textsubscript{v} decreased but this decrease was not statistically significant (Fig. 2c).

U\textsubscript{osm} decreased after medetomidine administration in the three treated groups. Significant differences from control values were seen at 60, 90, 120 min following injection (Fig. 2d).

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**Fig. 1.** The effects of medetomidine administered intravenously (IV; 20, 40 µg/kg) or: intramuscularly (IM; 80 µg/kg) on mean arterial blood pressure (MABP, mmHg). Values are mean ± standard error (SE), n=4. * Significantly different from control values (\(p<0.05\)).
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CH₂O showed a significant increase at 90 and 120 min for the 20 µg/kg dose and at 60, 90, 120 min for the 40 µg/kg dose whereas in dogs administered 80 µg/kg IM, CH₂O significantly decreased at 30, 60, 90 and 120 min (Fig. 2e).

FNa increased with all doses of medetomidine. Significant difference from respective control values were recorded at 60, 90 and 120 min in animals administered 80 µg/kg IM (Fig. 2f).

Plasma osmolality and plasma ADH concentrations:
Posm significantly increased along the whole experiment after injection of 40 µg/kg IV and 80 µg/kg IM (Fig. 3a). Plasma concentrations of ADH significantly decreased by IV injection and increased by IM injection (Fig. 3b).

Plasma glucose levels: Mean plasma glucose concentrations initially increased after medetomidine administration and subsequently decreased for all medetomidine doses (Fig. 4).

DISCUSSION

The present data have shown that IV administration of medetomidine produced biphasic effect on MABP, an initial increase lasted 5–15 min followed by a long-lasting decrease. The initial increase results from peripheral vasoconstriction due to stimulation of postsynaptic α₂-adrenoceptors [1, 2, 27], while the decrease is the result of activation of central and presynaptic α₂-adrenoceptors and the central effects usually override the peripheral ones [1, 8, 18]. In this study the initial hypertension was not seen when medetomidine was injected IM because the intramuscular administration dampens the increase in blood pressure seen with this class of drugs. The differences in the initial blood pressure response between the two routes are likely related to variations in the rate of drug concentration, which affect the activation of the peripheral adrenoceptors [29]. The increase was followed by a long-lasting decrease. Significant hypotension was never observed in this study after IV administration because of peripherally-induced vasoconstriction [27]. On the other hand significant hypotension was noted after IM administration of 80 µg/kg. Since the IM administration of α₂-agonists produces a less important stimulation of peripheral adrenoceptors, it might be associated with more prominent CNS hypotensive effects. In this work plasma medetomidine concentrations could not be measured. Previous studies however, have demonstrated that IM administration of medetomidine avoids the acute effects of peripheral vasoconstriction and subsequent hypotension.
hemodynamic changes seen with IV administration of the same dose, but results in similar hypotensive effect and undergoes same pharmacokinetic changes after the first 30 min [29, 34]. Medetomidine has not been found to induce any significant hypotensive effect after IM administered of much lower doses [24]. If this is the case, the significant hypotension observed in the present study following IM administration of 80 µg/kg could be attributed to a high dose.

In the study reported here renal responses to medetomidine varied greatly with different dosing routes in complete accordance with the overall changes that have occurred in MABP especially after the first 30 min. In a regard to this issue RBF and GFR increased following IV administration of medetomidine. These changes could be explained by preferential vasoconstriction of the peripheral arterioles that would increase glomerular hydrostatic pressure and thus GFR. A similar effect in dogs administered guanabenz; another potent α2-adrenoceptor agonist has been reported [30]. After IM administration of 80 µg/kg RBF and GFR decreased, which could be attributed to the significant decrease in MABP that resulted in a decrease in RBF and conceivably led to a decrease in GFR. These results are consistent with previous reports that have shown that dexmedetomidine, an active isomer of medetomidine decreases RBF in anesthetized dogs [17].

Uv markedly increased after IV administration of medetomidine, which is in agreement with the previous studies [5, 6, 11]. Uosm decreased due to increased urine volume. P_{osm} after IV administration of medetomidine was gradually increased. The increased production of dilute urine suggests that renal loss of water resulted in more concentrated serum. The mechanisms underlying the increased urine production after administration of α2-agonists are still controversial. Some possible mechanisms include, increase of RBF and GFR, inhibition of ADH release from posterior pituitary [6, 27, 30], inhibiting the release of insulin with the resultant glucosuria and osmotic diuresis [20, 32]. In the current experiment, urinary PAH and urinary creatinine concentration values (results not shown) did not show consistent changes suggesting that the increase in urine volume was due to causes other than increase in RBF and GFR. Plasma ADH levels were decreased gradually by IV administration of 20 and 40 µg/kg with a similar time course of the decrease in Uv. These results indicate that the decrease in plasma ADH is the main cause for increasing urine production. The increase in FNa is supporting this idea. Plasma glucose levels did not exceed the tubular maximum for glucose reabsorption; therefore osmotic diuresis does not appear to be a cause in the medetomidine-induced diuresis. Interestingly, Uv did not change after IM administration of 80 µg/kg that could be attributed to the increased conservative capacity of the nephron in response to the significant decrease in blood pressure. This interpretation is further supported by our data demonstrating that plasma ADH levels increased after this dose rate to reduce renal loss of water.

The present study was performed in healthy dogs with normal kidney functions and the results demonstrated that IV administration of medetomidine at dose rates of 20 and 40 µg/kg resulted in profound diuretic effects. The effects of medetomidine in animals with renal impairment is unknown but, clinically on the basis of these data if medetomidine temporarily has a polyuric effect on the renal patients as same as other diuretic agents, it seems to be safely administered to the renal patients as a pre-anesthetic drug avoiding them anuria produced by anesthesia.
ever this idea will be fully investigated in a fellow up study.
In summary we conclude that: 1) IV administration of medetomidine at dose rates of 20 and 40 µg/kg results in profound diuresis up to 2 hr; 2) Suppression of ADH release from the CNS is one of the mechanisms of medetomidine-induced diuresis although it may not be the principal one; 3) IM administration of medetomidine at a dose of 80 µg/kg has no diuretic action and this dose should be used with discretion due to its adverse effects on blood pressure and renal hemodynamic

REFERENCES