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The effects of 10% hypertonic saline, 0.9% saline and hydroxy ethyl starch infusions on hydro-electrolyte status and adrenal function in healthy conscious dogs ☆

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Abstract

The purpose of this study was to investigate the influence of different saline and colloid solutions on adrenal steroid secretion in dogs. Six healthy male Beagles underwent three infusion cycles: 10 min infusion of 30 ml/kg of NaCl 0.9%, 5 ml/kg of hydroxy ethyl starch, or 5 ml/kg of NaCl 10%. Plasma osmolality, hematocrit, total solids, cortisol and aldosterone levels were measured at 0, 5, 15, 30, 60, 120, 180 and 240 min after beginning infusion. Plasma ACTH levels were measured at 0, 15 and 240 min. An identical timing of sampling was applied during a control session omitting the fluid infusion. Osmolality, sodium, chloride and cortisol levels were found to be significantly higher with hypertonic saline solute compared to control. All fluid infusions lead to lowered plasma potassium, hematocrit, total solids and aldosterone values. ACTH concentrations did not show significant changes with any of the infusion cycles. The increase in cortisol levels suggests that hypertonic saline infusion could be interesting in critical care resuscitation, particularly in patients who are suffering from relative adrenal insufficiency.

Keywords: Adrenal steroids; Fluid infusion; Osmolality; Electrolytes; Dog

1. Introduction

The properties of saline and colloid solutions make them attractive resuscitation fluids (Smith et al., 1985; Tabacchi Fantoni et al., 1999; Oliveira et al., 2002a,b; Kreimeier and Messmer, 2002; Rozansky and Rondeau, 2002; Kramer, 2003; Vincent and Gerlach, 2004). The effect of fluid resuscitation on the immune system is a very active area of research. Serious injuries activate the immune system and may lead to development of the systemic inflammatory response syndrome. Adrenal secretion in general and cortisol in particular, are known modulators of the inflammatory and immune responses (Prigent et al., 2004a,b). In human patients, low cortisol levels during septic shock are associated with a poor prognosis (Annane et al., 2005). Interestingly, hypertonic saline solutions (HSS) have been reported to stimulate the hypothalamo–pituitary–adrenal axis (HPA) and to increase cortisol and adrenocorticotropic hormone (ACTH) concentrations in different species (Rittmaster et al., 1987; Bahr et al., 1988; Irvine et al., 1989; Dohanics et al., 1991; Rabinovici et al., 1992; Raskind et al., 1995; Cudd et al., 1998). Currently, the clinical or experimental applications of HSS (concentration, infusion rate and dosage) are not standardized (Wade et al., 1990; Yilmazlar et al., 2000). This variability leads to very heterogeneous experimental results regarding adrenal cortisol secretion. Finally, to the author's knowledge,

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only two previous reports described the effects of HSS infusion on aldosterone levels in healthy humans (Cross et al., 1989; Itagaki et al., 2001).

The information regarding cortisol, aldosterone and ACTH levels after infusion of HSS, colloid, or isotonic saline solution (ISS) has not previously been presented in the veterinary literature. To make up for this lack of data, we aimed to investigate and compare the influence of these solutes on the pituitary-adrenal axis in healthy conscious dog. Finally, we tried to define the relationships between adrenal secretion and hydro-electrolytic parameters to define the properties of each solute (osmolality, electrolytic composition, volume expansion capacity), which could influence cortisol, aldosterone and ACTH release.

2. Materials and methods

2.1. Animals

Six healthy male Beagles aged four to six years were included in this study. Body weight ranged from 9.8 to 12.2 kg (mean ± standard error of the mean (SEM), 11.3 ± 0.4 kg). These dogs were cared for according to the principles outlined by the Lyon College of Veterinary Medicine Ethics Committee. Before each cycle, all animals were fasted from midnight the day before. Water and food were withheld during the experiment.

2.2. Procedure

In this experimental prospective study, six dogs underwent four infusion cycles, separated by at least a three-week interval. The order of the studies was randomized. One cycle was a control protocol without any infusion, the three others differed in the fluid choice, hypertonic saline solution,[1] colloid,[2] or isotonic saline solution.[3] Two catheters were inserted in peripheral veins. One catheter was used for infusion of the fluid and the other was used for blood collection. The first heparinized blood sample (3 mL) was collected before infusion and considered as the 0 min value. Then, the HSS infusion (IV, 5 mL/kg at a flow rate of 0.5 mL/kg/min), the colloid infusion (IV, 5 mL/kg at a flow rate of 0.5 mL/kg/min) or the ISS infusion (IV, 30 mL/kg at a flow rate of 3 mL/kg/min) was started. At infusion completion, the catheter was removed. Seven heparinized blood samples (3 mL) were obtained at 5, 15, 30, 60, 120, 180 and 240 min after beginning the fluid infusion. Three blood samples were collected on EDTA at 0, 15 and 240 min. During the control protocol, the same schedule of blood sampling was used. EDTA blood samples were centrifuged and plasma was kept frozen at −20 °C until the ACTH assays were performed. For each heparinized blood sample, the following schedule of analysis was performed. Immediately after collection, 0.5 mL of heparinized whole blood was separated, put into micro tubes, centrifuged, and used to read hematocrit values on a paper scale. Then, total solids were measured on the serum using a refractometer.[4] The remaining 2.5 mL of heparinized blood was centrifuged and the plasma was separated. Plasma osmolality was determined by freezing point depression[5] on 50 μL of plasma. The remaining plasma was kept frozen at −20 °C until sodium, potassium, cortisol and aldosterone determination. Plasma sodium, chloride and potassium concentrations were measured using an ion-specific electrode system.[6] Cortisol, aldosterone and ACTH assays were analyzed based on a radioimmunologic method.[7,8,9]

2.3. Statistical analysis

All results are presented as mean ± SEM. A specific software was used for statistical analysis.[10] For each parameter, an area under the time-curve taken from 0 to 240 min ($AUC_{0–240}$) was calculated using a linear interpolation. Comparison between AUC obtained with the different protocols was performed using a one-way analysis of variance (ANOVA) followed by a Fischer's partial least-squares difference. Correlations across the different parameters variations were evaluated with Pearson's correlation coefficient between cortisol and aldosterone, and all other parameters for each experiment. The significance threshold was set at 0.05.

3. Results

3.1. Side-effects

No side effects were observed during the procedure, immediately afterwards or in the following weeks.

3.2. Electrolyte concentrations

All the infusions increased plasma sodium levels, and showed significant differences in $AUC_{0–240}$ as compared to the $AUC_{0–240}$ for the control protocol (Fig. 1, Table 1). Moreover, the sodium $AUC_{0–240}$ for the HSS infusion was significantly different from the $AUC_{0–240}$ for the ISS and colloid infusions. The HSS infusion induced immediate and persistent high sodium levels (144.2 ± 0.8 at 0,

[1] Hypertonic sodium chloride 10%, CEVA Santé Animale, Libourne, France.
[2] Plasmohès® (hydroxy ethyl starch in NaCl 0.9%), Aguettant, Lyon, France.
[3] Isotonic sodium chloride 0.9%, Aguettant, France.
[4] Réfractomètre, Atago, Japan.
[5] Cryogenic Osmometer, Roebling, Germany.
[6] Opti CCA; AVL, SCIL, Manheim, Germany.
[7] Cortisol RIA kit, Ortho Clinical Diagnostics, Roissy, France.
[8] Aldock-2 assay system, DiaSorin Inc., Stillwater, Minnesota, USA.
[9] ACTH ^{125}RIA Kit, DiaSorin Inc., Stillwater, MN, USA.
[10] StatView, SAS Institute Inc., Cary, NC, USA.

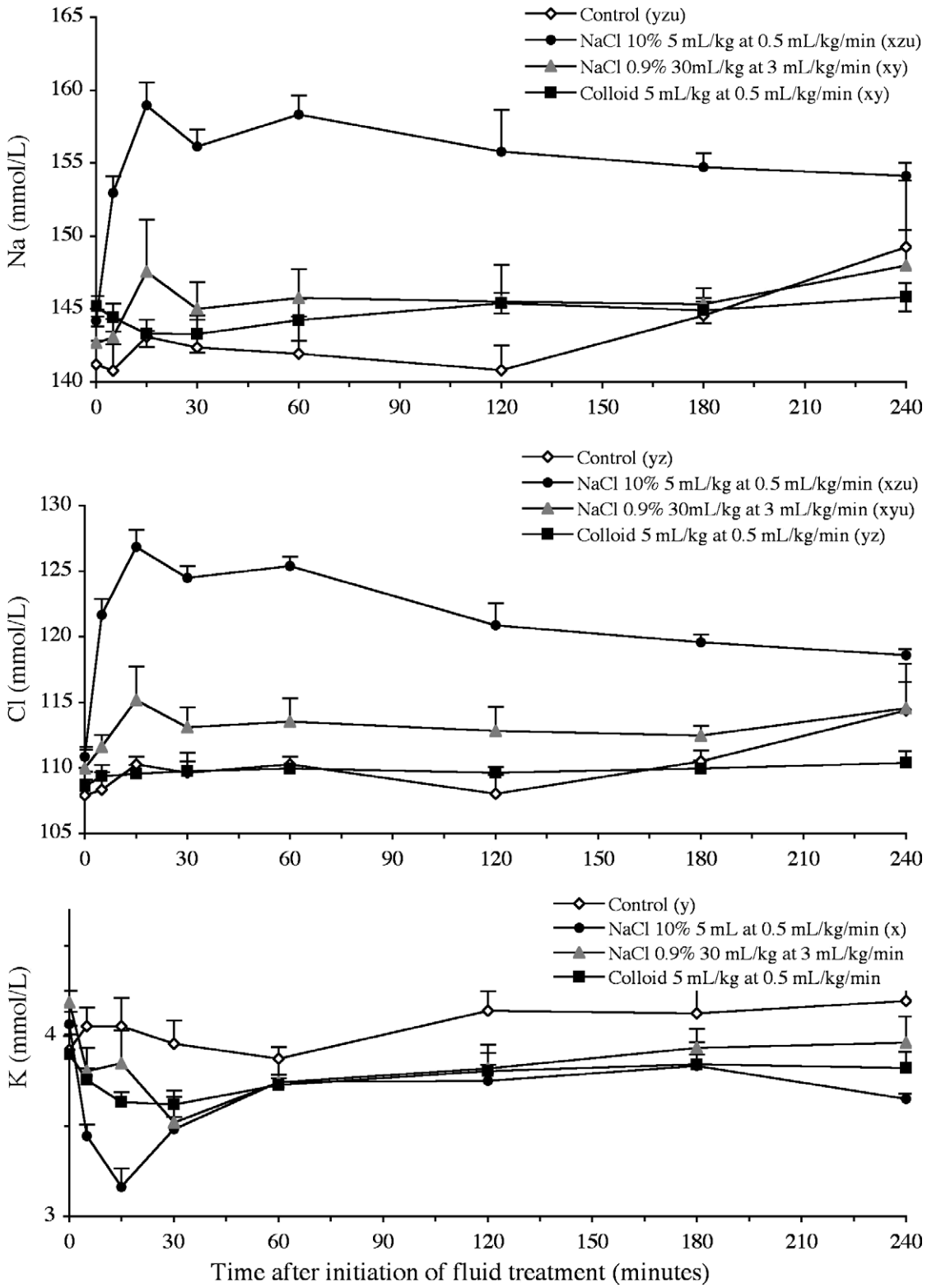

Fig. 1. Changes in plasma sodium (Na), chloride (Cl) and potassium (K) concentrations caused by NaCl 10% (5 mL/kg at 0.5 mL/kg/min), NaCl 0.9% (30 mL/kg at 3 mL/kg/min), colloid (Plasmohès® 5 mL/kg at 0.5 mL/kg/min), and in control protocol. Data are mean ± SEM ($n = 6$). Level of significance ($p < 0.05$). x: AUC_{0-240} different from control, y: AUC_{0-240} different from NaCl 10% infusion, z: AUC_{0-240} different from NaCl 0.9% infusion, and u: AUC_{0-240} different from colloid infusion.

153.0 ± 1.1 at 5, 159.0 ± 1.5 at 15 and 154.1 ± 0.5 mmol/L at 240 min). However concentrations remained under 160 mmol/L during the 240 min of the experiment.

Likewise, the HSS infusion induced persistent hyperchloremia (110.9 ± 0.5 at 0, 121.7 ± 1.2 at 5, 126.9 ± 1.3 at 15 and 118.6 ± 0.5 mmol/L at 240 min). The chloride

Table 1
Changes in AUC_{0-240} for NaCl 10% infusion (5 mL/kg at 0.5 mL/kg/min), NaCl 0.9% infusion (30 mL/kg at 3 mL/kg/min), colloid infusion (Plasmohès® 5 mL/kg at 0.5 mL/kg/min), and control protocol

AUC	Control	NaCl 10%	NaCl 0.9%	Colloid
Na	$26{,}364 \pm 140^{yzu}$	$37{,}387 \pm 294^{xzu}$	$34{,}387 \pm 205^{xy}$	$34{,}983 \pm 273^{xy}$
Cl	$26{,}433 \pm 201^{yz}$	$29{,}203 \pm 157^{xzu}$	$27{,}159 \pm 37^{xyu}$	$26{,}364 \pm 140^{yz}$
K	976 ± 21^{y}	887 ± 12^{x}	919 ± 27	904 ± 20
Osmolality	$73{,}340 \pm 356^{y}$	$78{,}123 \pm 319^{xzu}$	$74{,}551 \pm 1038^{yu}$	$72{,}121 \pm 578^{yz}$
Hematocrit	$10{,}215 \pm 389^{yz}$	9827 ± 305^{x}	9073 ± 229^{x}	$10{,}713 \pm 356$
Total solid	$14{,}151 \pm 556^{yz}$	$13{,}401 \pm 483^{x}$	$12{,}729 \pm 295^{x}$	$14{,}389 \pm 248$
Cortisol	285 ± 30^{yz}	602 ± 14^{xzu}	350 ± 102^{y}	235 ± 26^{y}
Aldosterone	$16{,}423 \pm 5967^{yzu}$	2615 ± 1489^{x}	4225 ± 1358^{x}	1555 ± 45^{x}

AUC Na: AUC_{0-240} for plasma sodium concentration in mmol/L/min.
AUC Cl: AUC_{0-240} for plasma chloride concentration in mmol/L/min.
AUC K: AUC_{0-240} for plasma potassium concentration in mmol/L/min.
AUC osmolality: AUC_{0-240} for plasma osmolality in mOsm/L/min.
AUC hematocrit: AUC_{0-240} for hematocrit variations in %/min.
AUC total Solid: AUC_{0-240} for total solid in g/L/min.
AUC cortisol: AUC_{0-240} for plasma cortisol in μg/dL/min.
AUC aldosterone: AUC_{0-240} for plasma aldosterone concentration in pg/mL/min.
[x] AUC_{0-240} different from this of control.
[y] AUC_{0-240} different from this of NaCl 10% infusion.
[z] AUC_{0-240} different from this of NaCl 0.9% infusion.
[u] AUC_{0-240} different from this of colloid infusion.

AUC_{0-240} with the HSS infusion was significantly different as compared to the AUC_{0-240} for the control protocol and for the ISS and colloid infusions. An elevation of plasma chloride levels was also observed with the ISS infusion, but its AUC_{0-240} differed significantly only from the AUC_{0-240} for the colloid infusion.

The HSS infusion induced a decrease in plasma potassium levels. The maximal effect was observed 15 min after initiation of infusion (3.16 ± 0.10 mmol/L at 15 min *versus* 4.07 ± 0.07 mmol/L at 0 min). The potassium AUC_{0-240} for the HSS infusion was significantly different from the AUC_{0-240} for the control protocol. The ISS and colloid infusions also lowered the plasma potassium levels, but the changes in AUC_{0-240} for these two solutes were not significantly different from the AUC_{0-240} for the control protocol and for the HSS infusion.

3.3. Hematocrit, plasma osmolality, or total solid concentrations

The plasma osmolality increased during the HSS infusion and remained elevated until the end of the experiment (Fig. 2). The osmolality AUC_{0-240} for the HSS infusion was significantly different from the AUC_{0-240} observed during all the other infusion cycles. As compared to the control protocol, the plasma osmolality increased with the ISS infusion and decreased with the colloid infusion. However, differences between AUC_{0-240} were not significant.

The HSS, ISS and colloid infusions decreased the hematocrit and total solid levels compared to the control protocol. Significant changes were only observed between the AUC_{0-240} for the HSS and ISS infusions and the AUC_{0-240} for the control protocol. The AUC_{0-240} did not differ significantly between the two test solutes.

3.4. Plasma aldosterone, cortisol and ACTH concentrations

The HSS, ISS and colloid infusions lead to decreased plasma aldosterone concentrations. The aldosterone AUC_{0-240} for all fluids was significantly different compared to the AUC_{0-240} for the control protocol. Surprisingly, during the control protocol, an increase in plasma aldosterone concentrations at 15 (96.0 ± 25.0 pg/mL) and 30 min (98.7 ± 29.3 pg/mL) was observed as compared to the baseline value (48.5 ± 16.4 pg/mL). We also noted important inter-individual variations in aldosterone (high SEM) for all of the administered infusions. We obtained low positive correlations between aldosterone and potassium changes (Pearson of 0.681 and 0.346, respectively for ISS and HSS), and between aldosterone and hematocrit (Pearson of 0.330 and 0.633, respectively for ISS and HSS).

The HSS infusion induced an increase of the plasma cortisol concentrations (Fig. 3). The cortisol AUC_{0-240} associated with the HSS infusion was significantly different from the AUC_{0-240} for the control protocol, and for the ISS and colloid infusions. The cortisol concentration increased immediately following the infusion of HSS (1.5 ± 0.3 at 0, 2.6 ± 0.5 at 5, and 3.6 ± 0.4 μg/dL at 15 min) and reached a maximum value at 30 min (4.5 ± 0.8 μg/dL). The ISS infusion also increased cortisol values, but the difference was not significant compared to the control or the colloid infusion protocol. With HSS infusion, the changes in cortisol values were very moderately correlated to changes in sodium values (Pearson: 0.633) and osmolality values (Pearson: 0.566). When restricted to the first 30 and 60 min, the correlation between cortisol and sodium changes reached a coefficient of 0.809 and 0.749, respectively (Pearson correlation). Applying the same restriction to the first 30 and 60 min, the correlation between cortisol

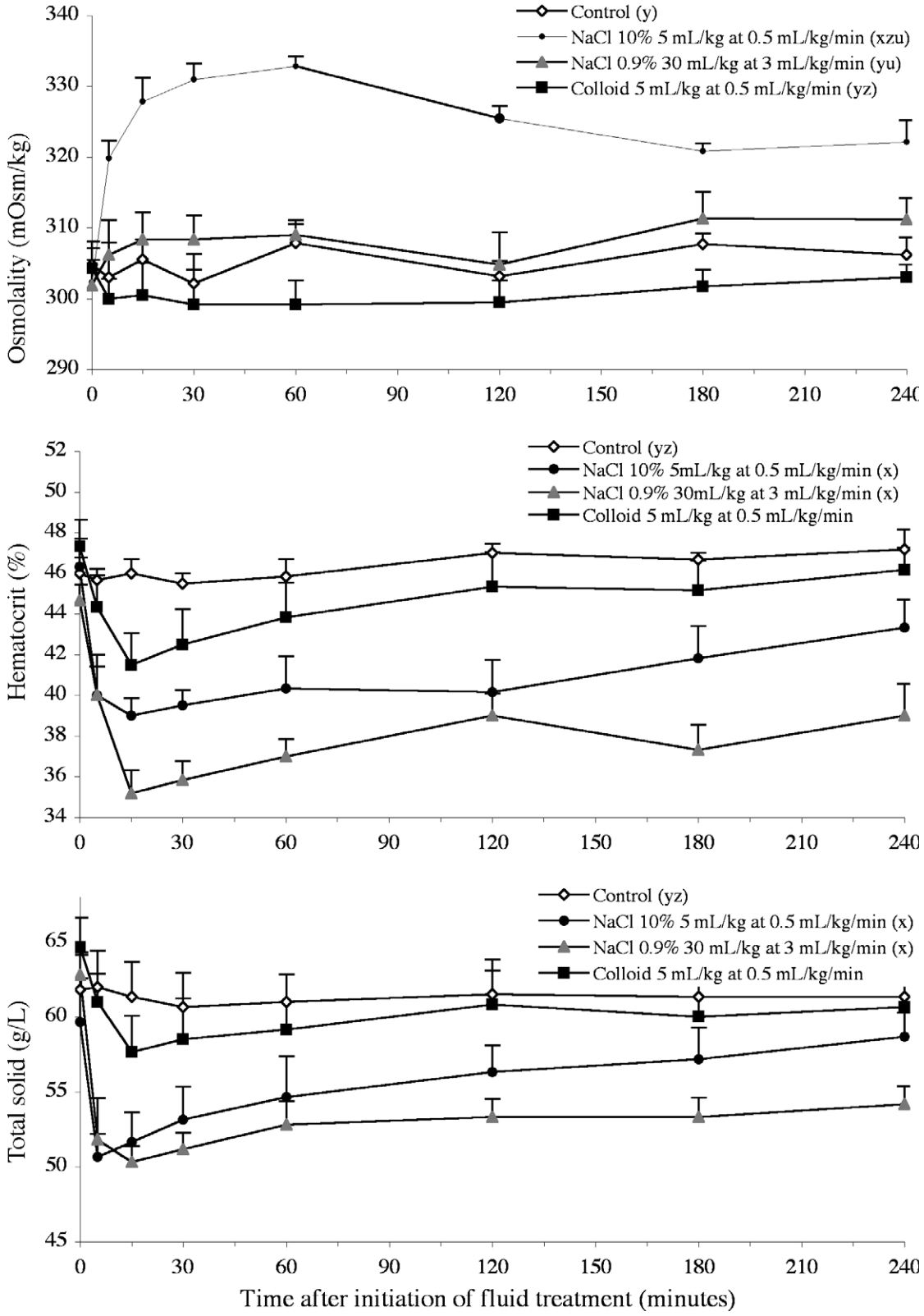

Fig. 2. Changes in hematocrit, plasma osmolality and in plasma total solid caused by NaCl 10% (5 mL/kg at 0.5 mL/kg/min), NaCl 0.9% (30 mL/kg at 3 mL/kg/min), colloid (Plasmohès® 5 mL/kg at 0.5 mL/kg/min), and in control protocol. Data are mean ± SEM ($n = 6$). Level of significance ($p < 0.05$). x: $AUC_{0–240}$ different from control, y: $AUC_{0–240}$ different from NaCl 10% infusion, z: $AUC_{0–240}$ different from NaCl 0.9% infusion, and u: $AUC_{0–240}$ different from colloid infusion.

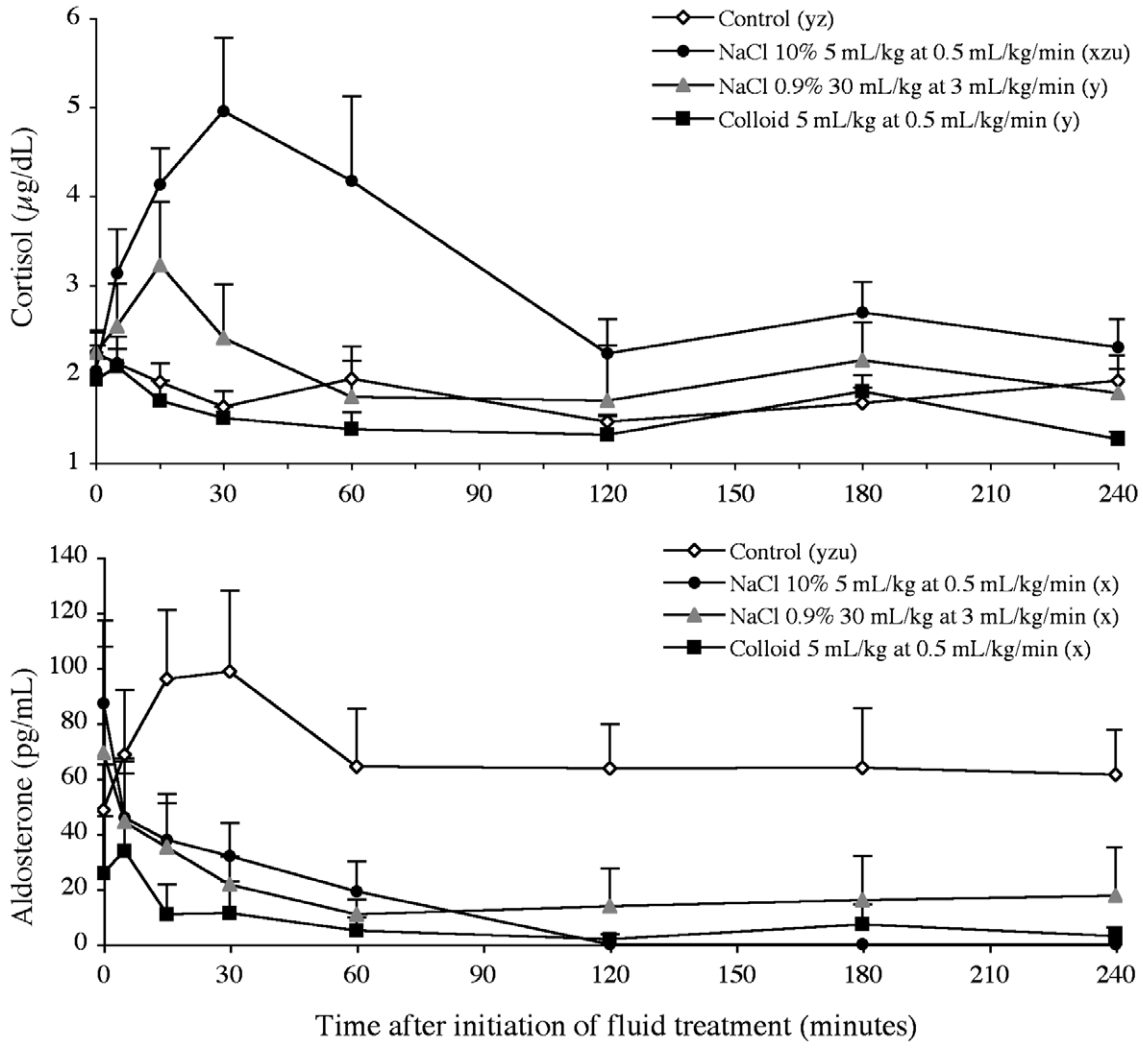

Fig. 3. Changes in plasma cortisol and aldosterone concentrations caused by NaCl 10% (5 mL/kg at 0.5 mL/kg/min), NaCl 0.9% (30 mL/kg at 3 mL/kg/min), colloid (Plasmohès® 5 mL/kg at 0.5 mL/kg/min), and in control protocol. Data are mean ± SEM ($n = 6$). Level of significance ($p < 0.05$). x: AUC_{0-240} different from control, y: AUC_{0-240} different from NaCl 10% infusion, z: AUC_{0-240} different from NaCl 0.9% infusion, and u: AUC_{0-240} different from colloid infusion.

and changes in osmolality showed a correlation coefficient (Pearsons) of 0.790 and 0.734, respectively.

ACTH values showed important inter-individual differences, and no significant differences were observed between protocols (Fig. 4).

4. Discussion

For this prospective experimental study we selected fluid volumes and rates routinely used and recommended in emergency and critical care practice (Kramer, 2003; Vincent and Gerlach, 2004). This study confirmed HSS generated hypernatremia resulting in a marked plasma hyperosmolality. The sodium elevation remained below the salt poisoning level of 160 mmol/L (Vassar et al., 1990; Schertel et al., 1996,1997; Tabacchi Fantoni et al., 1999; Khanna et al., 2000), and did not trigger any adverse effects. The observed persistent hypernatremia, hyperchloremia and plasma hyperosmolality throughout the entire infusion cycle despite the infusion cycle induced fluid shifts and dilution, has been previously reported in different studies (Schertel et al., 1996; Ajito et al., 1999; Cai et al., 2002). The effects of the two isotonic solutes (ISS and colloid) on plasma sodium, chloride and osmolality were less dramatic and related to the lower saline load provided by these fluid infusions.

In the present study plasma potassium levels decreased with all three infusions but only HSS was significantly different from control. The drop in potassium concentration observed with all infusions could be attributed to plasma dilution induced by solutes devoid of potassium. Moreover, hypernatremia and hyperosmolality could play a role in lowering plasma potassium levels because the lowest potassium values were observed with HSS infusion. This observation is unusual. Generally, an elevation in effective plasma osmolality due to hypernatremia results in a diffu-

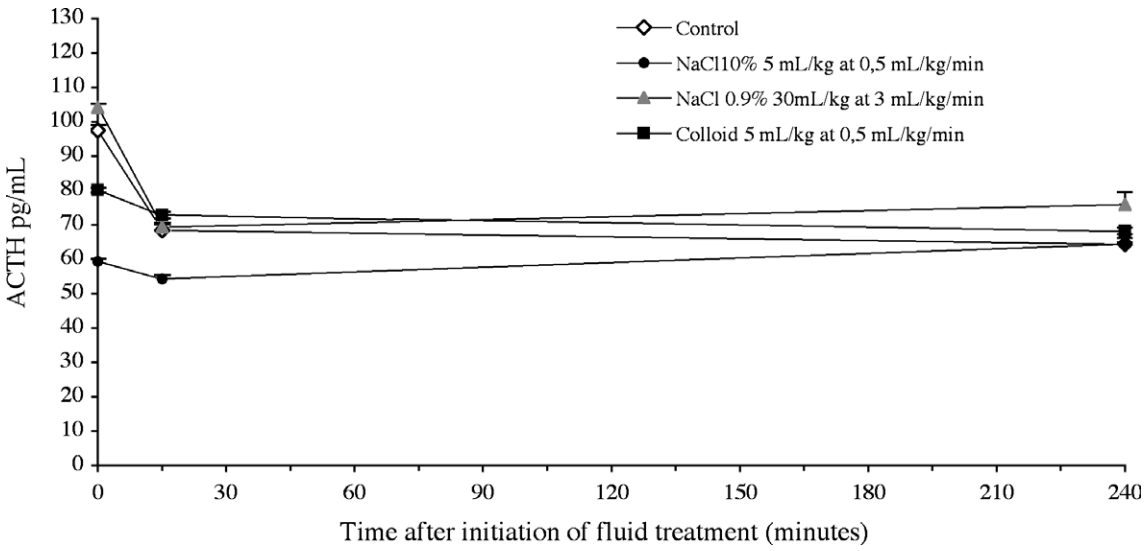

Fig. 4. Changes in plasma ACTH by NaCl 10% (5 mL/kg at 0.5 mL/kg/min), NaCl 0.9% (30 mL/kg at 3 mL/kg/min), colloid (Plasmohès® 5 mL/kg at 0.5 mL/kg/min), and in control protocol. Level of significance ($p < 0.05$). x: AUC_{0-240} different from control, y: AUC_{0-240} different from NaCl 10% infusion, z: AUC_{0-240} different from NaCl 0.9% infusion, and u: AUC_{0-240} different from colloid infusion.

sion of water out of the cells and contributes to a parallel movement of potassium out of the cells thereby elevating plasma potassium concentration (Rose and Post, 2001). However Qureshi and Suarez (2000) reported that the increased sodium load in the distal convoluted tubule should lead to an increased potassium loss in exchange for sodium as glomerulotubular balance is maintained, resulting in hypokalemia.

Aldosterone secretion and regulation depend on two major regulators: potassium concentration and activity of the renin–angiotensin system, and on two less potent regulators: the sodium concentration and ACTH levels. The direct effects of sodium are usually minimal and act through plasma osmolality. Hyperosmolality and/or volume expansion diminish renin–angiotensin system activity and consequently aldosterone secretion (Guyton and Hall, 2000). In the present study, volume expansion may explain the decrease in aldosterone for all infusions. In addition, for HSS infusions, the increased plasma osmolality contributed to decreases in plasma aldosterone concentration. Two previous reports described a decrease in aldosterone levels in healthy humans with HSS infusion (Cross et al., 1989; Itagaki et al., 2001). Decreased potassium levels could also contribute to the lowering effect on circulating aldosterone. ACTH levels did not change and could not be incriminated. Of note, aldosterone levels variability for control protocol, which was previously described, showed an important individual variability (Cartledge and Lawson, 2000; Feldman and Nelson, 2004). Despite this variability, solute infusion effects were clearly observed.

HSS infusion caused a significant increase in plasma cortisol concentration in this study. Elevation in cortisol with HSS infusion has previously been reported in healthy humans (Rittmaster et al., 1987; Bahr et al., 1988; Raskind et al., 1995; Elias et al., 1997), rats (Dohanics et al., 1991), horses (Irvine et al., 1989), sheep (Cudd et al., 1998), however the mechanism for this elevation is currently not fully understood. In our study, we compared the effects of different solutes in order to determine which kind of stimulus (i.e. osmolality and plasma sodium concentration increase or volume expansion) could be responsible for cortisol release. ACTH is the major determinant of cortisol secretion. Most of the studies investigating HHS report an increase in cortisol concentrations in association with high ACTH levels (Rittmaster et al., 1987; Bahr et al., 1988; Taylor, 1999). However, Raskind et al. (1995) observed high cortisol levels and non-significant ACTH variations in healthy human patients treated with NaCl 5%. Interestingly, in our study, the ACTH concentrations did not exhibit increases in all the infusion protocols tested and remained unchanged even before and during the cortisol elevation in the HSS infusion experiment. These results do not sustain the hypothesis that ACTH is implicated in adrenal cortisol release induced by HSS infusion. Considering the correlated elevations of plasma cortisol, sodium and osmolality in the first 30 min following HSS administration, and the lack of significant effect on cortisol release with the two isotonic solutes, a mechanism involving vasopressin (AVP) has been suggested. Moreover, HSS infusion (NaCl 20%) has been demonstrated to increase AVP secretion in dogs (Van Vonderen et al., 2004). Finally, several studies have shown a secretagogue effect of AVP on cortisol either through the hypothalamic corticotropin releasing factor (CRF) or directly through ACTH (Buckingham et al., 1992; Hauger and Aguilera, 1993; Mazzocchi et al., 1997; Taylor, 1999). In our study, the absence of elevated ACTH levels does not sustain the hypothesis of hypothalamo–pituitary–adrenal axis activation by AVP suggested by Rittmaster et al. (1987) and Bahr et al. (1988). A direct adrenal effect of AVP on cortisol release could be hypoth-

esized. Grazzini et al. (1998) reported the presence of AVP receptors in the adrenal cortex and their involvement in cortisol secretion in many species including humans and rats. Additionally, reports available in dogs demonstrate the physiological relevance of the stimulatory effect of AVP on the adrenal glucocorticoid production (Brooks and Blakemore, 1989).

The small sample size and the wide variability of some parameters are limitations in this study and add a higher level of difficulty in interpretation of results. In addition, considering the lack of recent reference in dogs, respective ACTH and AVP involvement in adrenal secretion must be hypothesized very carefully.

This original study addressing the effects of different solutes on adrenal secretion in the healthy dog provides a first statement in the field. Dog is novel in inception. Further investigation is recommended to simultaneously measure AVP, ACTH and cortisol plasma levels during an HSS infusion and investigate their coordinated changes.

5. Conclusion

This study identifies new information concerning the effects of HSS, ISS and isotonic saline colloid solutions on cortisol release, aldosterone and ACTH levels in healthy dogs. All fluid infusions lead to a decrease in plasma aldosterone levels. Cortisol release depended on the sodium fluid content and its effect on plasma osmolality. HSS infusion induced a significant cortisol release, ISS effect was less dramatic while a decrease in plasma cortisol concentrations was observed with colloid infusion. We did not demonstrate any implication of ACTH. Parallel increased in cortisol secretion, plasma osmolality, and sodium concentrations suggested a contribution of AVP. Further studies are necessary to investigate AVP secretion during hypertonic fluid infusion and mechanisms involved. The potential adrenal secretagogue effect of AVP on cortisol is interesting in clinical practice particularly in the relative adrenal insufficiency described during the septic shock.

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