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EFFECT OF ANGIOTENSIN-CONVERTING ENZYME INHIBITOR ENALAPRIL ON SYSTOLIC BLOOD PRESSURE OF THE CAMEL

(With 3 Figures)

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تأثير مثبط الإنظيم المحول لأنجيوتنسين (إنالابريل) على ضغط الدم الانقباضي في الجمال

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تمت دراسة تأثير إنالابريل (مثبط الإنظيم المحول لأنجيوتنسين) على ضغط الدم الانقباضي في الجمال العربية. تم تقسيم عشرة جمال إلى مجموعتين بكل مجموعة خمسة جمال. حقنت المجموعة الأولي بجرعة تحتوي على ٠,٢ مايكروجرام/١٠٠كجم إنالابريل عن طريق العضل وتركت المجموعة الثانية كمجموعة ضابطة. تم قياس ضغط الدم الانقباضي قبل وبعد ٢, ٤, ٨ , ١٢ و ٢٤ ساعة بعد الحقن كما تم جمع عينات دم في نفس فترات قياس ضغط الدم وذلك بغرض تحديد تركيز الصوديوم و البوتاسيوم في المصل, تناضحية الدم وكذلك لقياس نشاط إنظيمات رينين و أنجيوتنسين II وآرجنين –فازوبرسين في المصل. أدى حقن إنالابريل إلى انخفاض حاد في ضغط الدم الانقباضي كما انخفض تركيز الصوديوم و تناضحية الدم و نشاط أنجيوتنسين II. كذلك أدى حقن إنالابريل إلى خفض تركيز البوتاسيوم و نشاط إنظيم رنين و آرجنين–فازوبرسين في المصل. لهذا تم التوصل إلى أن آرجنين–فازوبرسين الداخلي ونظام رينين–أنجيوتنسين يلعبان دورا هاما في المحافظة على ضغط الدم في الجمال.

SUMMARY

The effect of Enalapril (angiotensin-converting enzyme inhibitor, ACE-I) on systolic blood pressure was studied on the Arabian camel *(Camelus dromedarius)*. Ten camels were divided into two groups of five animals each. Group one animals were injected each with 0.2µg/100 kg Enalapril im, and those of group two were kept as untreated controls. Systolic

blood pressure was measured before and at 2, 4, 8, 12 and 24 hours after treatment. Blood samples were concurrently collected with the blood pressure measurements for the determination of plasma concentration of sodium, potassium, plasma osmolality, renin activity (PRA), angiotensin II and arginine-vasopressin (AVP). Enalapril induced a sharp decrease in systolic blood pressure, lowered plasma [Na^+], plasma osmolality and angiotensin II. It also increased the concentration of [K^+], renin activity (PRA) and arginine-vasopressin (AVP) in the plasma. It is concluded that endogenous AVP and renin-angiotensin system plays an important role in maintaining blood pressure in camels.

Key words: *Angiotensin-Converting Enzyme-Systolic Blood-Pressure Camel.*

INTRODUCTION

The ability of the Arabian camel to endure heat stress and water deficiency has been reported by many workers (Schmidt-Nelsen, 1964; Finberg et al., 1978; Macdonald, 1984; Achaaban et al., 1992; Al-Qarawi, 1997). The cardiodynamics of the dromedary camel (*Camelus dromedarius*) under normal, stress or anesthesia is poorly reported in the literature.

The angiotensins are a group of peptides produced by the action of renin. Renin is an acid protease (aspartyl protease) synthesized and secreted by the juxtaglomerular apparatus of the kidney (Ganong, 1993). The secreted renin cleaves its substrate angiotensinogen (a circulating α2-globulin synthesized by the liver) to produce angiotensin I. Angiotensin-converting enzyme cleaves two terminal amino acids from angiotensin I, to form angiotensin II, an octapeptide. Angiotensin-converting enzyme is present in most endothelial cells with highest concentration in the lungs (Ganong, 1993; Leslie et.al. 1995; Guyton and Hall, 1996). Usage of pharmacological agents that block the conversion of angiotensin I to angiotensin II through inhibition of angiotensin converting enzymes, such as Captopril and Enalapril, has helped in studying the functions of angiotensin II as well as the effects of hypotension on animals.

The effect of lowered blood pressure, as predisposed by hypotensive drugs, shock, anesthesia or stress factors, on camels is not well documented. This experiment was conducted to study the effect of

Enalapril on blood pressure, plasma electrolytes, osmolality, PRA, angiotensin 11 and AVP in the Arabian camel.

MATERIALS and METHODS

Animals

Ten 3-5 year old, one-humped camels (*Camelus dromedarius*), (5 males; 5 non-pregnant and non-lactating females), weighting 458 ± 28 kg (mean ± SEM) were used in the experiment. The camels were confined in a special farm. They were fed on a daily ration of 5 kg barley and 3 kg hay, and water was provided *ad libitum*. The camel's ages were determined by dentition marks and the records of the owner.

Experiment Design

The camels were randomly assigned to two groups of 5 camels each. Group 1 animals were injected each with Enalapril while group 11 animals were kept as undosed controls. Enalapril, (0.2 µg / 100 kg) (SIGMA, St. Louis, MO, USA), an angiotensin-converting enzyme inhibitor (ACE-I), was given by the intramuscular (IM) route.

Arterial blood pressure was measured before and at 2, 4, 8, 12, and 24 hours after Enalapril injection by a Doppler ultrasound (811 series, Parks Medical Electronics, USA) using the coccigeal (tail) artery.

Blood samples were collected from the jugular vein immediately before and at 2, 4, 8, 12, and 24 hours post-treatment for the measurements of plasma concentrations of Na+, K+, osmolality, plasma renin activity (PRA), angiotensin II, and arginine-vasopressin (AVP). Ten ml of blood was collected in heparinized tubes for measurements of plasma concentrations of Na+, K+, and osmolality. The plasma was separated by centrifugation (1,000 × g) at +4 °C and analyzed within 24 hours. Plasma concentrations of Na+ and K+ were analyzed using Beckman auto-analyzer Synchron CX-5 Clinical System (Beckman, USA). Plasma osmolality was measured by freezing point depression using advanced 3C2 Osmometer (Advanced Instruments, MA, USA).

For hormone analysis, 30 ml of blood was collected into pre-chilled tubes containing K3-EDTA. The blood was centrifuged at +4 °C and the plasma was stored at (-20 °C until assay. Radio-immunoassay (RIA) kits were used to determine plasma angiotensin II and AVP (Buhlmann, Basil, Switzerland), plasma renin activity (PRA) (INCSTAR, Stillwater, MN).

Values are expressed as means ± SEM. Analysis of variance (ANOVA) was used to determine the treatment and time effect. The treatment × time interaction used to determine the effect of time. The conservative F value was used to establish significance for the effect of treatment and time. Tukey's test was used to test for differences between means of end points for which the ANOVA indicated a significant ($p < 0.05$) F ratio.

RESULTS

Fig. 1 shows the effect of Enalapril on the systolic blood pressure during the 24 hours post administration. Following administration of the drug, the blood pressure dropped to reach minimal values at 4 hours post-treatment. It then gradually started to rise, but maintained significantly lower than the controls.

The effect of Enalapril on plasma sodium and potassium concentrations and plasma osmolality is shown in Figure 2. The drug produced a decrease in plasma sodium and osmolality and an increase in plasma potassium. Plasma sodium was significantly lowered after drug administration reaching minimum (134.6 mmol/l) at 4 hours post-treatment. It started to rise thereafter, but was maintained significantly lower until 12 hours and it reached normal values (150.4 mmol/l) at 24 hours post-treatment. On the other hand, plasma potassium peaked 4 hours after treatment to reach 5.3 mmol/l, and was maintained significantly high until 8 hours after treatment. It then returned to normal values of 4.5 mmol/l at 24 hours post-injection. Plasma osmolality was reduced after Enalapril treatment reaching minimum values (277.9 mosmol/kg) at 4 hours after treatment. It was maintained significantly low at 8 hours and then gradually rose to reach pretreatment levels (309 mosmol/kg) at 24 hours post-injection.

The results of changes in the concentrations of PRA, AVP and AII in plasma after Enalapril treatment is given in Figure 3. Following the administration of the drug, plasma PRA and AVP were increased and that of AII was lowered. Plasma PRA and AVP concentrations were increased steadily (1.55 ngAI/ml/h and 1,34 pg/ml respectively) to peak at 4 hours after treatment. Thereafter they started to drop, but maintained signifhigher for 12 and 8 hours respectively, to reach normal values (0.90 ngAI/ml/h and 0.74 pg/ml respectively) at 24 hours post-injection. However, plasma AII activity dropped after treatment and reached minimum of 0.57 pg/ml at 4 hours post-treatment. It was maintained

significantly lower than normal values until 12 hours and then it rose gradually reaching pre-treatment values of 1.1 pg/ml in 24 hours (Fig. 3).

DISCUSSION

There is no previous report describing the effect of angiotensin II inhibitors on the blood pressure of camels. The decrease in systolic blood pressure was a direct consequence of angiotensin inhibition by Enalapril. These results are consistent with those reported previously by Davidai et al., (1984), Morganti et. al., (1987), and Wade et al., (1987) in human, and by McDougall, (1987) in sheep. The decrease in plasma angiotensin II during converting enzyme inhibition interrupts the short feedback loop existing between plasma angiotensin II and renin, and causes an increase in plasma PRA (Mortensen and Williams, 1995). The changes in plasma electrolytes and osmolality after ACE-I administration described in this study are similar to those reported for sheep (McDougall, 1987).

The effect of Enalapril on plasma electrolytes and osmolality is thought to be brought about by angiotensin II reduction resulting in lowering of Aldosterone level. Aldosterone is the major mineralocorticoid synthesized and secreted by the glomerulosa cells of the adrenal cortex. It has an important role in regulating electrolyte balance by increasing Na+ reabsorption and K+ excretion in many of body tissues, including the kidney, sweat glands, salivary glands, and colon and thus aids in the regulation of the body fluid volume. (Ganong, 1993; Swensson and Reece, 1993; Leslie et al., 1995). Many factors have been shown to be involved in the control of aldosterone secretion including: angiotensin II, adrenocorticotropic hormone (ACTH), plasma K+ concentrations, and to a lesser extent, plasma Na+ concentrations (McDougall, 1987; Griffin and Ojeda, 1992; Ganong, 1993; Leslie et. al., 1995).

In our study, the increase in AVP was attributed to the hypotension induced by Enalapril. AVP secretion is initiated by reduced blood pressure, reduced blood volume and/or increased plasma osmolality (Share, 1996).

In conclusion, administration of the drug Enalapril at a dose rate of 0.2 μg/kg to the Arabian camel induced a sharp decrease in angiotensin II in plasma. This was resulted in decreased systolic blood pressure, lowered plasma [Na^+] and decreased plasma osmolality. It also

increased plasma [K^+] concentration, plasma renin activity (PRA) and arginine-vasopressin (AVP) concentration. It seems that endogenous renin-angiotensin system and AVP play an important role in maintaining the blood pressure of camels.

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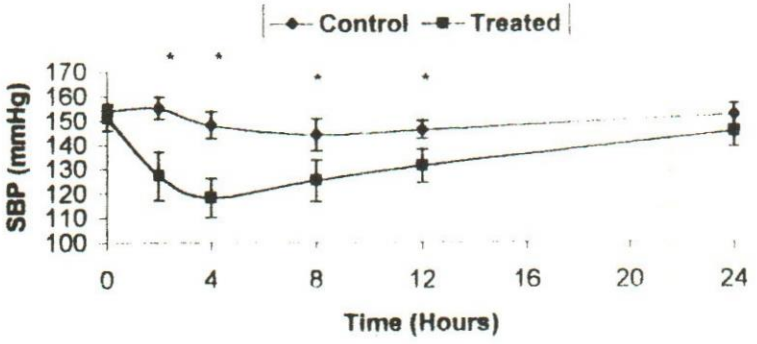

Fig. 1. Changes of systolic blood pressure following ACE-I administration (n = 5). Data are expressed as means ± SEM; *P < 0.05, compared with the respective group at the corresponding time.

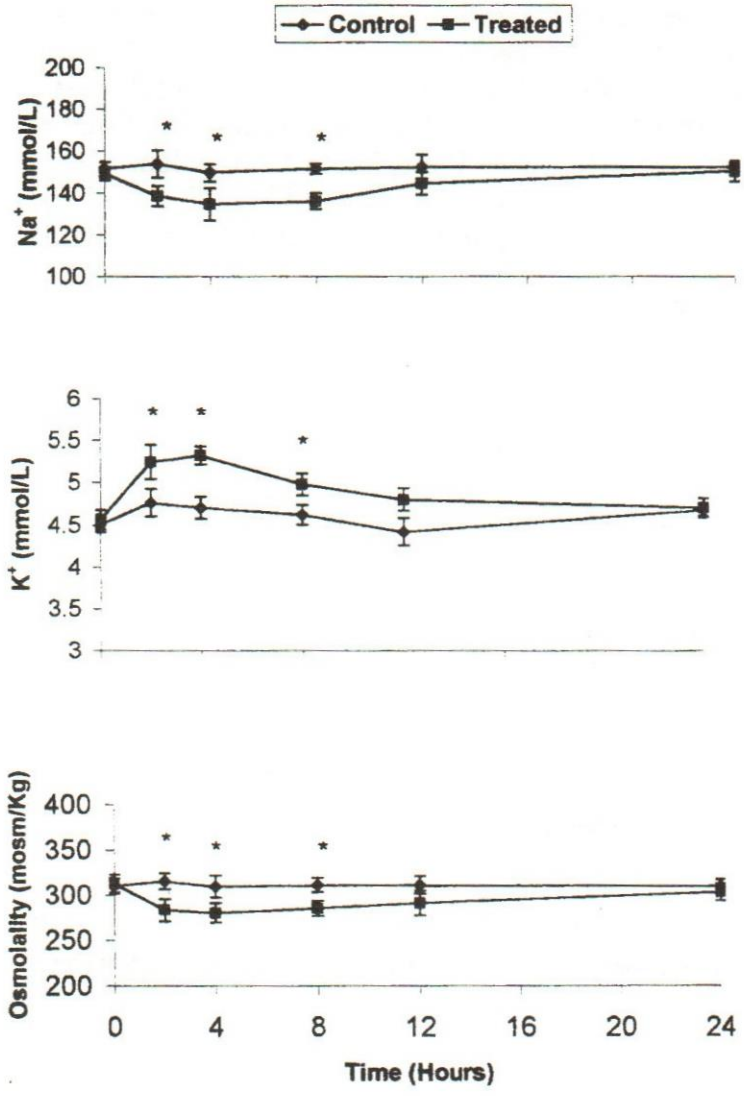

Fig. 2. Changes of plasma Sodium, potassium and osmolality following ACE-I administration (n = 5). Data are expressed as means ± SEM; *P < 0.05, compared with the respective group at the corresponding time.

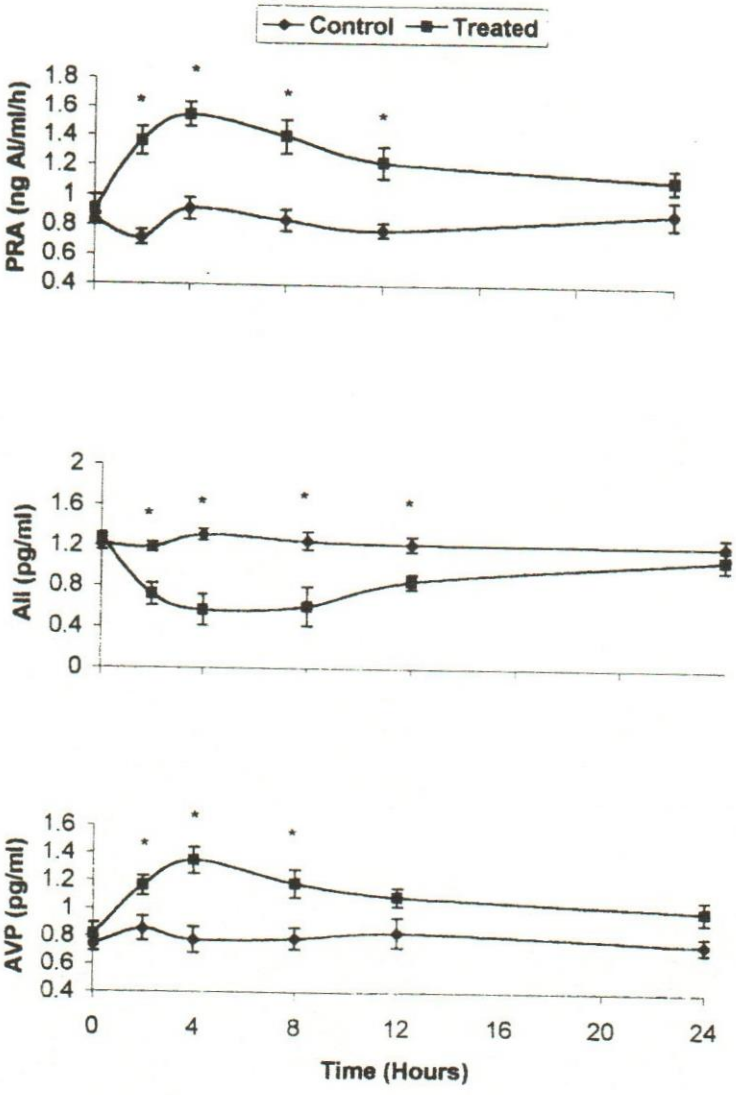

Fig. 3. Changes of plasma renin activity (PRA), plasma angiotensin II (AII) and plasma arginine vasopressin (AVP) following ACE-I administration (n = 5). Data are expressed as means ± SEM; *P < 0.05, compared with the respective group at the corresponding time.