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EVALUATION OF CLINICAL AND BLOOD BIOCHEMICAL EFFECTS OF DEXAMETHASONE IN GOAT SPECIES

S. Bughio[1], T. A. Qureshi[1], E. I. S. Daraghmah[1], M. Malhi[2] and A. Tunio[3]

[1]Department of Veterinary Pharmacology, [2]Department of Veterinary Physiology and Biochemistry, [3]Department of Veterinary Surgery,
Sindh Agriculture University Tandojam, Pakistan

ABSTRACT

Dexamethasone, a member of glucocorticoides, is commonly used in the treatment of various metabolic and inflammatory disorders and in emergency situations in farm animals. Beside its beneficial effects, the drug has potential adverse effects associated with high doses and long-term therapy. This study was carried out to evaluate the clinical and blood biochemical effects of dexamethasone administered intramuscularly at the high dose rate of 4 mg kg^{-1}. Body weight for 5 days in goats. Blood samples were collected before and on day 5 after the last drug administration at different time points for 96 h. The results showed that dexamethasone administration increased pulse rate at 1, 2, 3, 4, 48 h and at 5, 6, and 24 h as compared to 0 h. Respiratory rate increased at 2, 3 and 24 h and at 4, 5, 6 h post dexamethasone administration compared to pre-administration (0 h). During the experiment, polyuria, polydipsia, polyphagia, defecation and weight loss were noticed in all animals. Serum glucose concentration (mg/dl) increased significantly at 1, 6, 12 and 24 h post administration of dexamethasone. Serum concentrations (mEq/L) decreased for phosphorus from 1–12 h, and for potassium from (1–48 h) at various time points after treatment compared to pre-treatment (0 h). However, serum sodium level remained unchanged before and after the treatment. In conclusion, intramuscular administration of high dosed dexamethasone exerted significant effects on clinical and biochemical parameters in goats, which were drug associated and the values returned to normal as the drug cleared from the body.

Keywords: BIochemical, clinical, dexamethasone, glucocorticoides, goats.

INTRODUCTION

Goat is one of the most important specie of the livestock, which contributes to the nutrition and health of several million people in developing countries particularly in the subcontinent by providing highly valued animal protein. It is an animal of

Corresponding author: shams_bughio@yahoo.com

developing countries and 90% of goats are found in Asia and Africa (Economic Survey of Pakistan, 2006). Corticosteroids comprise one of the most beneficial and widely used groups of medications in veterinary medicine. Dexamethasone (DEX) is a commonly used synthetic immunosuppressant drug, belongs to glucocorticoides (GC) and its action is approximately 20- 30 times more than the cortisol. GC translocated from the cytosol of the target cells to the nucleus, where it attaches to particular glucocorticoid receptors within the regulatory DNA sequences and ultimately, transcriptionally adjusts the expression of GC reactive genes (Pascussi *et al.,* 2003; Sonneveld *et al.,* 2007). DEX possesses antioxidant properties based on the declined level of malondialdehyed (MDA) and increase of catalase (CAT) and glutathione peroxidase (GSH-PX) and superoxide dismutase (SOD), in both tissues and plasma (Ayse *et al.,* 2010).

A number of studies with different doeses have been conducted on exogenous dexamethasone in different animal species to examine its effects on various systems of the body (Maddux e*t al.,* 1988; Vernon and Taylor 1989; Wasfi *et al.,* 1990). DEX may cause elevation of blood pressure, salt, water retention, hypophosphatemia, hyperglycemia, increase in urine flow, glomerular filtration rate (GFR) and increase in the blood glucose level (Lopes *et al*., 2004; Karen *et al.*, 2005). Its high dose produced a potential side effect by increasing calcium excretion and causing low levels of potassium by increasing the excretion of potassium via the kidneys (Peek, 2003; Tumelo, 2006). DEX improved pulmonary function and increased systolic and diastolic blood pressure by reducing capillary permeability and increasing vasoconstriction in various animal species (Susan *et al*., 2003; Daniel *et al.*, 2005; Shahab *et al*., 2006).

To substantiate adverse effects of short-term administration of high dosed exogenous dexamethasone, assessment of its biochemical and clinical effects should be carried out in order to know its clinically safe level in goats. In our conditions, such studies have not been conducted at large especially in ruminants. Considering the importance and widespread use of dexamethasone in veterinary clinics in our environment, this study was designed to investigate some biochemical and clinical effects in goat specie, related with short-term administration of high dose of exogenous dexamethasone.

MATERIALS AND METHODS

Six healthy adult goats of mixed breed weighing 20 kg average BW were used in this study. All goats studied were approved by Sindh Agriculture University, Tandojam, Pakistan, Animal Care and Use Committee and were kept at Department of livestock, Faculty of Animal Husbandry and Veterinary Sciences. All the experimental animals were dewormed and vaccinated against enterotoxaemia, contagious pleuropneumonia and then acclimatized to a local environment for a period of 4 weeks. The standard feeding regimen was followed during the experiment. Dexamethasone (Dexafar: Farvet) was administered intramuscularly (I/M) in six goats once daily for 5 days at the dose rate of 4 mg kg^{-1} BW. Clinical parameters i-e. pulse rate (beats/minute), respiration rate (times/minute) and rectal temperature (^{o}F) were examined before the

administration of drug (0 h) and at 1, 6, 12, 24, 48, 72 and 96 h post drug regimen administration. Pulse rate was determined by auscultation of heart sounds with a stethoscope and the respiratory rate was determined by observing thoraco-abdominal movements with each respiration. During the experiment, animals were watched carefully for observable clinical signs i-e. polyuria, polydipsia, polyphagia, defecation and for weight loss. On day 5, blood samples were collected in sterile test tubes before the administration of drug (0 h) and at 1, 6, 12, 24, 48, 72 and 96 h post drug regimen administration. Blood samples were centrifuged for 10 min at 4000 rpm and serum was collected. The serum was analyzed for glucose (mg/dl) using the human Kit (Gesellschaft fur Biochemia mbH Im Maisel 4.d-6420.Wiesbaden, Germany). Sodium (meq/L) and phosphorus (meq/L) were determined using colorimetric method through sodium reagent set (TC. Tech-co, Inc.Rochester Hills Michigan, Wiesbaden, Germany) and potassium (meq/L) was determined using Potassium rapid Kit (Ingo test. Ingelheim, Wiesbaden, Germany).

Data were analyzed using the statistical software (Graph Pad Prism USA) for analysis of variance (ANOVA) and the differences were considered significant at $P<0.05$. The Tukey Karmer multiple comparison test was used to compare the means.

RESULTS

In this study, administration of dexamethasone I/M for 5 days at the dose rate of 4 mg kg^{-1} BW in goat significantly increased pulse rate ($P<0.05$) at 1, 2, 3, 4, 48 h and ($P<0.01$) at 5, 6, 24 h post dexamethasone administration. A maximum increase of pulse rate was noted at 5 h but this increased response was gradually returned to normal by 72 to 96 hours (Table 1). The respiration rate was significantly increased ($P<0.05$) at 2, 3, 24 h and ($P<0.01$) at 4, 5, 6 h post dexamethasone treatment. A maximum increase of respiration rate occurred at 6 h post dose administration. The respiration rates then gradually returned to normal by 48 hours (Table 2), whereas, the rectal temperature was not significantly affected by dexamethasone administration. This non-significant increase in rectal temperature was noticed up to 24 hours with a maximum increase at 5 hour (Table 1).

It was observed that DEX administration showed clinical effects in goats. A prominent effect, polyuria was seen in all animals. The increased urination and defecation was observed for about 12 hours, which then returned to normal (Table 3). Polyphagia was noted in all the experimental animals. Excessive eating behavior continued for about 12 hours after each dose of dexamethasone (Table 3). Condition of polydipsia was also noticed in all animals that were continued for 12 hours during and after dosage regimen (Table 3). Decrease in the body weight (Average 2 kg/ animal) occurred in all animals and was observed after 48 hours from the start of the dexamethasone that lost for about 8 days (Table 3).

Biochemically, dexamethasone administration revealed a significant increase in serum glucose level (P< 0.01) at 1, 6, 12 and 24 h (Table 2). The maximum significant effect on glucose was observed at 1h post dexamethasone administration. A significant decrease in serum phosphorus was observed (P<0.05) at 1, 6 and (P< 0.01) at 12 h (Table 2). The maximum decrease of serum phosphorus level was noted at 12 h post treatment. Whereas, significant decrease in serum potassium was found (P< 0.01) at 1, 6, 12, 24 and 48 h (Table 2). The maximum decrease in serum potassium level was noted at 12 h post drug treatment. Furthermore, it was also found that the serum sodium level was increased non-significantly after dexamethasone administration in goat (Table 2). This non-significant maximum increase in the serum sodium level was observed at 12 hours following drug treatment. Afterward, serum sodium level gradually returned towards the baseline at 96 hrs post dexamethasone administration.

Table1. Effects of short-term I/M administration of dexamethasone on some clinical parameters in goats.

Time (h)	Pulse Rate (Beats/minute)	Respiration rate (Times /minute)	Rectal Temp. (ºF)
0	79.16 ± 1.07	21.00 ± 0.73	102.06 ± 0.22
1	84.33 ± 1.95*	22.16 ± 0.87	102.21 ± 0.15
2	85.50 ± 1.92*	25.16 ± 1.26*	102.24 ± 0.13
3	86.16 ± 1.81*	26.50 ± 1.76*	102.31 ± 0.08
4	86.33 ± 1.92*	28.10 ± 1.85**	102.40 ± 0.09
5	89.83 ± 1.25**	28.20 ± 1.97**	102.43 ± 0.07
6	89.50 ± 1.08**	28.58 ± 1.78**	102.25 ± 0.05
24	89.50 ± 0.87**	26.00 ± 1.86*	102.17 ± 0.07
48	86.83 ± 1.83*	23.81 ± 1.25	102.13 ± 0.04
72	81.00 ± 1.00	23.42 ± 1.08	102.11 ± 0.01
96	80.33 ± 0.80	22.80 ± 0.54	102.10 ± 0.02
Mean	85.31 ± 3.76	25.06 ± 2.62	102.21 ± 0.21

Values are mean ± SE, Different from 0 at *P< 0.05 and **P< 0.01.

Table 2. Effects of short-term I/M administration of dexamethasone on some serum biochemical parameters in goats.

Time (h)	Glucose (mg/dl)	Phosphorus (meq/L)	Potassium (meq/L)	Sodium (meq/L)
0	71.5 ± 1. 00	7.69 ± 0.23	11.78 ± 0.35	141.16 ± 1.07
1	202.0 ± 4.31**	5.15 ± 0.25 *	8.60 ± 0.83**	142.03 ± 1.24
6	191.8 ± 2.83 **	5.15 ± 0.31*	6.77 ± 1.72**	142.63 ± 1.47
12	182.6 ± 2.52 **	4.88 ± 0.39**	5.97 ± 0.78**	143.83 ± 1.04
24	134.8 ± 1.21 **	6.29 ± 0.42	6.53 ± 1.94**	141.83 ± 0.88
48	82.2 ± 2.74	7.22 ± 0.52	7.16 ±1.37 **	140.61 ± 2.14
72	79.9 ± 2.61	7.72 ± 0.70	10.25 ± 1.86	140.08 ± 2.27
96	72.1 ± 1.30	7.74 ± 0.82	11.21 ± 0.20	141.66 ± 0.61
Mean	127.11±57.68	6.48±1.26	8.53±2.27	141.72±1.17

Values are mean ± SE, Different from 0 at *P< 0.05 and **P< 0.01.

Table 3. Clinical signs observed following short-term I/M administration of dexamethasone in goats.

Animal ID No.	Symptoms/signs shown
All animals	Polyuria
All animals	Polydipsia
All animals	Polyphagia
All animals	Defecation
All animals	Weight loss

DISCUSSION

Corticosteroids are key regulators of whole body homeostasis that provide an organism with the capacity to resist environmental changes and invasion of foreign substances. The current study revealed that the short-term intramuscular administration of dexamethasone showed significant effect on some clinical as well as on biochemical parameters in goat. A significant increase in pulse and respiratory rate was noticed at post dexamethasone administration. The results of this study are in line with the findings of various studies where it was reported that pulse rate increased after dexamethasone treatment in humans (Greenough *et al*., 1992; Fauser *et al.,* 1993; Smets and Vanhaesebrouck 1996; Doyle *et al*., 2000; Daniel *et al*., 2005; Shahab *et al*., 2006), in sheep (Josine *et al*., 2005), in lambs (Segar *et al*., 2001) and in elephants (Susan *et al*., 2003). It is reported that corticosteroids affects the cardiovascular system as a result of their influence on plasma volume, electrolyte retention, epinephrine synthesis, and angiotensin levels, which together result in the maintenance of normal blood pressure and cardiac output. Corticosteroids have effects on myocardial responsiveness, arteriolar tone, and capillary permeability (Holland *et al*., 2003). All of these mechanisms singly or jointly affect the cardiac activity and may increase the pulse rate. Respiratory rate was significantly increased (Table 1) at various timings in goats; this was in line as reported previously (Yoder *et al*., 1991; Courtney *et al*., 1992; Ohlsson *et al*., 1992; Lee *et al*., 1999; Durand *et al*., 2002) in humans and animals. Furthermore, a study in a fetal sheep showed increased respiration that is reported to the glucocorticoid induced increased pulmonary angiotensin conversion enzyme (ACE) (Zimmermann *et al*., 2003). It is stated that ACE inactivates the vasodilators bradykinin and kallidin in the kallikrein-kinin system, by cleaving its primary metabolite bradykinin into it. The shorter fragment causing increase respiration rate and pulse rate (Sivieri *et al.,* 2007). Dexamethasone causes reduction in IL-1 and tumor necrosis factor α through inhibitory effects on nuclear factor κB may improve respiration by reducing pulmonary and circulating levels of pro-inflammatory cytokines (Annane *et al.,* 2006; Meduri *et al.,* 2007). In the current study, these pro-inflammatory mediators are supposed to be decreased following dexamethasone administration resulting an increased respiratory rate. In this study, DEX caused an excessive urination as well as defecation in all animals with this condition animals showed polydipsia (Table 3). These results are consistent with the findings reported in dog (Frony, 2004), and in elephants (Mikota and Plumb, 2006). It is reported that the DEX affect catecholamines principally the

epinephrine. It stimulates β2 receptors, which enhance epinephrine release; as a result, relaxation in the uterine smooth muscle takes place which develops the condition of excessive urination as well as defecation (Holland *et al*., 2003). Another possibility of increased water intake and excessive urination is this that, aldosterone initiated from adrenal cortex and it is involved in sodium/potassium regulation. The increased water and urine excretion reflects the direct compensation of the dexamethasone induced aldosterone deficit that is supposed to develop these conditions in this study. A decrease in the body weight was noted in all experimental animals (Table 3). The results of this study are in line as reported by others (Ohlsson e*t al.*, 1992; Frony, 2004). Altered GC levels can lead to muscle abnormalities and bone loss, but the condition usually associated with chronic hypercorticism. It was reported that increased level of glucocorticoid causes wasting of muscle and it is because of their catabolic effects on protein metabolism. Corticosteroid insufficiency results in decreased work capacity of striated muscle, weakness, and fatigue (Holland *et al*., 2003). Due to this, it is expected that DEX developed all these conditions in the present study causing decreased body weight in all experimental animals.

In our study dexamethasone administration showed significant increase in serum glucose level (Table 2). The results of this study are in agreement with several studies, where it was noticed that the treatment with dexamethasone caused a significant increase in serum glucose level in goat (Maddux e*t al.,* 1988), sheep (Vernon and Taylor 1989), camel (Wasfi *et al.,* 1990), pigs (Hellstern *et al*., 1996) and in human (Yeh *et al*., 1997). It is reported that increased hepatic gluconeogenesis/ glycogenesis is due to direct effects of GC on the hepatic expression of genes that code for enzymes required for glucose and glycogen biosynthesis (Holland *et al*., 2003). It is stated that GC stimulates the conversion of protein to carbohydrate through gluconeogenesis and promote the storage of carbohydrate as glycogen (Sousa, 2005). It also increases urinary nitrogen and this increase in urinary nitrogen following glucocorticoid administration is the result of amino acid mobilization from protein and its subsequent breakdown as a source of carbon during gluconeogenesis. Consequently, this breakdown of protein, converted into glucose is presumed to increase serum glucose level in the present study.

Moreover, significant decrease in the serum phosphorus level was observed (Table 2). These results are in agreement with researchers who reported that the treatment with dexamethasone caused a significant decrease in the serum phosphorus level (Maddux e*t al.,* 1988; Wasfi *et al.,* 1990; Hans *et al*., 2006). Parathyroid hormone (PTH) is the most important endocrine regulator to maintain phosphorus concentration in the extracellular fluid. It was reported that exogenous dexamethasone in animals stimulates a rise in circulating intact PTH (Guo *et al*., 2001). PTH may increase the fractional delivery of phosphate from the proximal tubules and increases phosphate excretion resulting decreased phosphorus level.

In this study, it was perceived that the serum potassium level was significantly decreased (Table 2). These results are in agreement with several researchers

who reported that the treatment with dexamethasone caused a significant decrease in serum potassium in camel (Wasfi *et al.,* 1990) and in humans (Peek, 2003; Karen *et al*., 2005; Tumelo, 2006). Dexamethasone has been shown to cause severe excretion of potassium in urine due to osmotic diuresis as a result of drug-induced hyperglycemia resulting decreased potassium level (Peek, 2003; Tumelo, 2006). It has been reported that the corticosteroids increased the excretion of potassium because they have a direct effect on the kidney (Holland *et al*., 2003). Due to this, in the present study, may be the dexamethasone directly influenced the kidney causing increased excretion of potassium resulting decreased potassium level in goats.

This study further elaborates that the serum sodium level showed same increasing trend but, it was not significantly increased after the administration of dexamethasone (Table 2). These results are in agreement with several studies in which it was reported that the treatment with dexamethasone caused a non-significant increase in serum sodium level (Maddux e*t al.,* 1988; Wasfi *et al.,* 1990; Karen *et al*., 2005). Prolonged aldosterone treatment results in sodium "escaping," a cessation of sodium changes, while potassium and hydrogen loss continues to occur (Holland *et al*., 2003). They reported that GC increase water diuresis, renal plasma flow and glomerular filtration rate (Holland *et al*., 2003). Due to this, an increase in sodium retention may occur with DEX administration along with an increase in sodium levels.

CONCLUSION

It can be concluded that the administration of dexamethasone intramuscularly for 5 days at the dose rate of 4 mg kg^{-1} BW in goat produces significant effects on various systems of the body, but these effects were not adverse in its intensity. All changes in studied parameters were drug related and values returned to base line by 48-96 hrs post dosage regimen. The results of this study will guide in the proper use of high dose of this drug in goats.

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