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Full Length Article

Residual Potential of Dexamethasone and its Effect on Goat Milk

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Abstract

The aim of this study was to analyse the effect of intramuscular administration of dexamethasone (DXM) on clinical, residual and milk composition parameters in goat. For this, 0.5 mg/kg BW dose of DXM was administered once daily for 3 consecutive days. Milk samples were collected before and after drug administration at 2, 8, 16, 32, 48, 72, 96, 120, 144, 168 h. Pulse rate and respiratory rate were increased ($P < 0.05$) in at 2, 8, 16, 32, 48 and 72 and 96 h While, the rectal temperature was increased ($P < 0.05$) only at 02 h post drug administration. The highest residual level of DXM was noticed at 32 h (2.70 ng/mL) and lowest at 168 h (0.25 ng/mL) in milk. Milk Fat increased ($P < 0.01$) at 32, 48 and 72 h and ($P < 0.05$) at 2, 8, 16, 96,120 h and then gradually returned to pre-treatment value at 144 h. The mean milk protein level was increased ($P < 0.01$) at 8, 16, 32, 48, 72 and 120 h and ($P < 0.05$) at 2 and 96 h. Milk Solid Not Fat level was increased ($P < 0.05$) at 16, 32, 48, 72 and 96 h, however, at 120 h this increase was ($P < 0.01$). Milk yield decreased ($P > 0.05$) from 2 – 16 h as compared to control then, decreased ($P < 0.05$) at 32, 48, 72, 96, 120, 144 h post DXM administration. It has been concluded that the therapeutic dose of DXM 0.5 mg/kg BW once daily for 3 consecutive days produced significant effects on clinical, residual level and milk composition parameters in goat.

Keyword: Dexamethasone; Goat; Milk; Potential; Residues

Introduction

Milk secretion from mammary glands is the main characteristic of all female mammals. The natural milk is important for young ones because it contains complete nutrients like carbohydrates, proteins, minerals and vitamins in an appropriate amount with little bit variation among various species of animals (Roadhouse and Henderson 1950). Within a particular specie, genetic factors, environmental conditions such as climate and stage of lactation may also affect the composition of milk. Usage of various drugs may also affect the quantity and quality of milk. Among drugs, corticosteroids are commonly used agents in Animals. Corticosteroids are a big group of naturally occurring and synthetic chemical compounds used in veterinary as well as in human medicine. Corticosteroids are immunosuppressive, anti-inflammatory and also important for carbohydrate, lipid metabolism, regulation of blood pressure and maintenance of muscle tone and bone density (Kufe *et al.* 2003).

Among corticosteroids, Dexamethasone is a synthetic corticosteroid and has pharmacological effects including anti-inflammatory, anti-toxic, anti-allergic and anti-rheumatic activities. Therefore, it is widely used in veterinary clinical treatment of maternal metabolic diseases to treat infectious diseases and it is also one of the commonly used drugs in livestock. However, DXM can also cause certain adverse reactions to animals, such as gastrointestinal reactions, allergic reactions, liver dysfunction, skin and mucosal symptoms. Therefore, DXM is strictly forbidden to be used as a growth hormone in animal-derived food globally. Many countries and organizations have established the maximum residue limits (MRLs) for DXM in animal foods (Li *et al.* 2021). (DXM) is commonly used as a therapeutic as well as in in high doses to treat chronic inflammatory and autoimmune diseases, some neurological disease and to prevent hypersensitivity reactions associated with certain medications (Sousa 2005; Ito *et al.* 2006). It has been reported that the long-term use of low concentrations of DXM may have adverse effects on public health (Becker 2011; Reig *et al.* 2016). DXM residues has been reported in the various biological samples such as urine, feces, meat, milk and liver in different animals (Chen *et al.* 2011; Cherlet *et al.* 2014). Importantly, their therapeutic use has also been restricted because of its concentration above the maximum residue limits (MRLs) in milk and edible tissues. The MRLs of DXM in milk samples are 0.3 μg/kg. Reportedly, DXM residues may also affect milk composition in various species

(Macrina *et al.* 2014). Due to the frequent use of DXM in various illnesses, it may produce residues in dairy and other products of animal origin aimed for human consumption. Hence, it is necessary to develop comprehensive control measures to monitor DXM residues in goat milk because goat milk is commonly consumed by children. Considering the limited information on DXM residues its effects on clinical and on the milk composition, this study was designed to assess the residual potential of DXM, its effects on clinical and on the milk composition in local goat breeds.

Materials and Methods

Experimental Protocol

Six lactating healthy goats of mix breeds were used in present study. The goats were kept indoor at Livestock Experimental Station, Sindh Agriculture University Tandojam. The animals were acclimatized for three weeks. All animals were dewormed and vaccinated before start of the experiment. All animals were identified by the use of an ear tag assigned a number from G1 to G6. Dexamethasone (DXM) (Dexafar, Farvet Pharmaceutical company) was administered intramuscularly to evaluate its residual profile and its effect on clinical and on goat milk composition.

Treatment procedure

Milk samples were collected before as a control and after drug administration. DXM was administered at a therapeutic dose of 0.5 mg/kg BW intramuscularly (I.M.) for 03 consecutive days once daily to six healthy lactating dairy goats (based on high yield lactating animals). Then, milk samples were collected at 2, 8, 16, 32, 48, 72, 96, 120, 144 and 168 h post drug administration. Milk samples were collected in two set of test tubes, one set containing 5 mL for residual analysis which was kept at -35°C until analysis and another set of test tube having 100 mL for milk composition which was analyzed immediately. The effect of DXM on milk composition and its analysis was investigated at the Department of Animal Products Technology, Sindh Agriculture University, Tandojam. For residual analysis, milk samples were brought in ice bags to Veterinary Research Institute Peshawar, Khyber Pakhtunkhwa.

Clinical parameters

Vitals: Pulse rate (PR), Respiratory rate (RR) and rectal temperature (RT) recorded before administration of DXM and after 2, 8, 16, 32, 48, 72, 96, 120, 144 and 168 h post dosage regimen respectively.

Analysis of milk

Fat content: For the determination of fat content, Gerber method was used as described by Kleyn *et al.* (2001). Briefly, 11 mL milk sample was mixed with 10 mL of 90% sulfuric acid and 01 mL amyl alcohol in Butyrometer and then closed with a rubber cork. The Butyrometer was placed in a Gerber machine and centrifuged for 05 min at 1100 rpm. The percentage of fat was identified on the scale of butyrometer.

Protein content: Protein content determination was carried according to Barbano *et al.* (1999). Briefly, a 05 mL milk sample was used in Micro-Kjeldahl digester in the existence of catalyst 0.2 g $CuSO_4$ and 02 g Sodium/Potassium Sulphate where 30 mL H_2SO_4 was used. The digested sample was diluted by adding 250 mL distilled water. Subsequently, 05 mL diluted sample was taken and distilled with 40% of Sodium hydroxide using Micro-Kjeldahl distillation unit where steam was distilled in 05 mL of 2% H_3BO_3 (Boric acid) containing an indicator for 03 min. The Ammonia trapped in H_3BO_3 and was determined by titrating with 0.1 N HCl. The Nitrogen Percentage was analyzed using the formula written as under:

$$N\% = \frac{1.4\ (V1 - V2) \times normality\ of\ HCl}{Weight\ of\ taken\ sample\ \times Volume\ of\ Blank\ Sample} \times 250$$

Where;
V1=Value of titrated milk sample
V2= Value of titrated blank sample

Protein content was evaluated by modifying nitrogen percentage to protein, believing that, all nitrogen was available in milk as a protein ie, protein percentage = N% × conversion factor. Conversion factor = 100/N% in milk products (*i.e.*, 15.66).

Lactose content: Milk Lactose determination was done through difference method using the following formula: Lactose% = TS% - (Fat% + Protein% + Ash%)

Solid not fat content (SNF): Determination of SNF content in milk was performed by difference method using following formula: Solid Not Fat%= TS% - Fat%

Residual detection: The residues of DXM in goat's milk were determined using Direct Competitive ELISA (AgraQuant® COKDA0800) according to manufacturer's instructions.

Statistical analyses

Statistical analysis was performed using a computer program, Student Edition of Statistic (SXW), Version 8.1 (Copyright 2005, Analytical Software, USA). Further, data were analyzed by linear models, where analysis of variance with three- way ANOVA was done in case of significant difference existed; the means were additional computed applying least significant difference (LSD) test at 5 and 1% probability level.

Results

This study was aimed to observe various effects associated with the short-term administration of dexamethasone (DXM) in goat species.

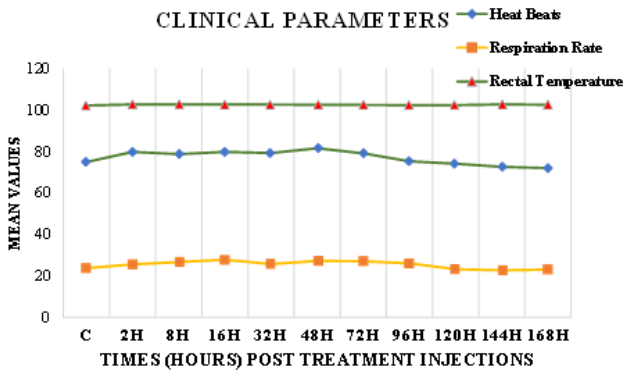

Fig. 1: Mean values of Clinical Parameters of goats (n=6) obtained after I/M administration of dexamethasone

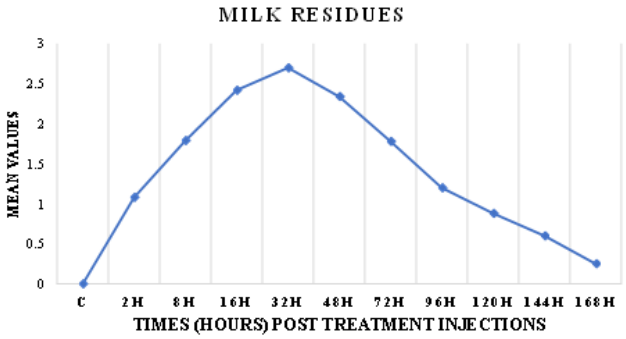

Fig. 2: Residue analysis of intramuscularly administered dexamethasone at the therapeutic dose of 0.5 mg/kg BW once daily for 3 consecutive days in goat (n=6) milk

Clinical parameters

Heartbeat, respiratory rate, rectal temperature

Pulse rate was increased ($P < 0.05$) at various time-points from 8 – 96 h however, it was decreased ($P < 0.05$) at 168 h as compared to control. The respiratory rate was increased ($P < 0.05$) at 2 h and at 8, 16, 32, 48, 72 and 96 h ($P < 0.01$) post-DXM administration. The maximum increase of respiratory rate was noticed at 16 h after treatment. Afterward, the respiratory rate gradually returned to control value at 168 h. The rectal temperature was increased ($P < 0.05$) at 02 h post-treatment, while, this increase was ($P > 0.05$) in subsequent hour in comparison to control (Fig. 1).

Dexamethasone residues in milk

Administration of DEX increased ($P < 0.01$) its residual level at 02, 08, 16, 32, 48, 72, 96, 120 and 144 h. However, statistical analysis showed ($P > 0.05$) increased value at 168 h. The highest and lowest mean values of DEX residues in goat milk were found at 32 and 168 h following DEX administration respectively (Fig. 2).

Effect of dexamethasone on the composition of milk

Milk fat: DXM administration increased ($P < 0.05$) milk fat content at 2, 8, 16, 96 and 120 h as compared to control whereas, this increased ($P < 0.01$) was perceived at 32, 48 and 72 h. The highest and lowest mean values of milk fat were noticed at 48 and 144 h post drug administration respectively. The milk fat values at 144 and 168 h were found statistically ($P > 0.05$) as compared to control (Fig. 3).

Milk protein: DXM administration increased ($P < 0.05$) at 2 and 96 h, whereas, at 8, 16, 32, 48, 72 and 120 h increased ($P < 0.01$) milk protein level. The highest and lowest mean values of milk protein level were detected at 48 and 144 h post drug administration respectively. At 144 and 168 h, the values showed a non-significant difference with the control value (Fig. 3).

Milk sugar (lactose): The therapeutic dose of DXM showed the ($P > 0.05$) - in milk lactose level at all designated time points of observations as compared to control (Fig. 3).

SNF: The administration of DXM increased ($P < 0.05$) at 16, 32, 48, 72 and 96 h, however, at 120 h, this increase was ($P < 0.01$). Then, the values at 144 and 168 h gradually returned to pre-treatment level and were found ($P > 0.05$) as compared to control value. The highest and lowest mean values of SNF were apparent at 120 and 168 h post drug administration respectively (Fig. 3).

Milk yield: DXM-induced effects caused decreased ($P > 0.05$) in milk yield 2–16 h (203.83 ± 9.27), as compared to pre-treatment observations, thereafter, a significantly decreased ($P < 0.05$). However, milk yield returned to control value at 168 h (206.67 ± 9.60) in lactating goats (Fig. 4).

Discussion

In current study, DXM at therapeutic dose of 0.5 mg/kg BW once daily for 03 days was administered intramuscularly to observe its residual, clinical and its effects on milk composition in goats. It was noticed that clinical indicators *i.e.*, pulse rate, respiration rate and rectal temperature (Fig. 1) were increased following the administration of DXM. The current study showed agreement with previous studies where it was also described (Becker 2011) that corticosteroids exhibits its effects on CVS as a result of its effect on plasma volume, and electrolyte balance , synthesis of adrenaline and angiotensin levels, all of which leading in maintaining normal blood pressure and cardiac output. Corticosteroids have effects on the heart muscle responses, permeability fluid and electrolyte balance concerned with proper carbohydrate, lipid metabolism, regulation of blood pressure, and bone density (Becker 2011). The increase in pulse rate (cardiac output) as well as the blood pressure has also been reported with DXM treatment. Increase in pulse rate and blood pressure have been observed in infants

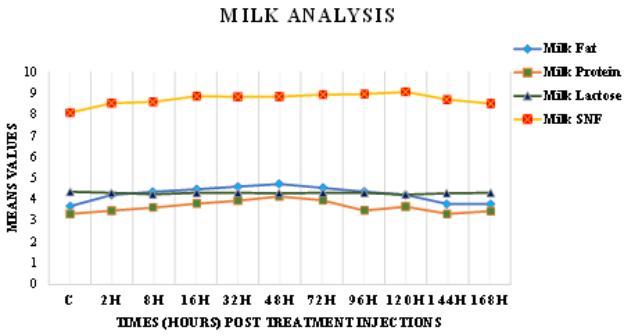

Fig. 3: Mean values of Milk analysis of goats (n=6) obtained after administration of I/M dexamethasone once daily for 03 days

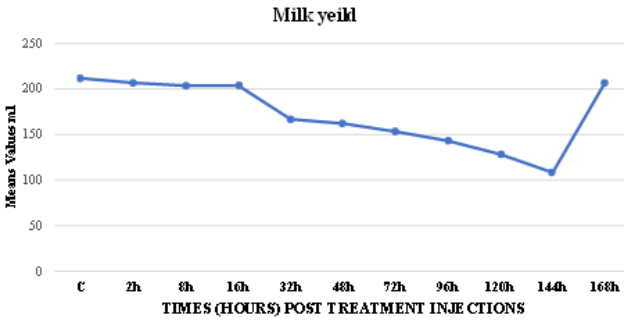

Fig. 4: Mean values milk yield of goats (n=6) obtained after administration of I/M dexamethasone

(Fauser *et al.* 1993; Washburn *et al.* 2003). The increase in respiratory rate in this study is also in accordance with the previous findings reported by Ohlsson *et al.* (1992) and Durand *et al.* (2002)) in humans and animals. It was stated that glucocorticoids have a positive inotropic effect on the cardiopulmonary system. It stimulates heart muscle contraction and increases heart rate, this increase in heart rate and cardiac output increases the volume of blood flow (Washburn *et al.* 2003). This increased blood flow with CO_2 crosses blood brain and blood CSF barriers. CO_2 combines with H_2O to form $H2CO_3$ that dissociates into HCO_3 Ions and H^+ ions. This H^+ stimulates chemo-sensitive area (Carotid bodies at the bifurcation of common carotid arteries). It has been reported in fetal sheep that the increased respiration and blood pressure in part is related to the glucocorticoid-induced increased pulmonary angiotensin conversion enzyme (ACE) (Zimmermann *et al.* 2003). The increase in rectal temperature in this study is supported by previous findings of Coelho *et al.* (1995) and Yared *et al.* (1998). It was reported that DEX treatment, either before or after endotoxin injection markedly inhibits temperature because of increased plasma interleukin and prostaglandin. In contrast to this, the non-significant effects on present study probably show the effect of DXM independent to temperature. It is possible that the mild increase in temperature in this study is presumably due to the inhibition or the release of many biologically active substances by DXM. These results are also consistent with the results reported in the dog (Bughio *et al.* 2015) and in elephants (Mikota and Plumb 2013).

Residual analysis

Following DXM administration once daily for three days, noticed its residues in goat milk at 2, 8, 16, 32, 48, 72, 96, 120 and 144 h (Fig. 2). The present results are supported by previous similar findings of Chen *et al.* (2011) and Cherlet *et al.* (2014). Draisci *et al.* (2001) reported residues of DEX in biological samples *i.e.*, urine, feces, meat, liver or milk in various animals. Besides the clinical usage of DXM in relieving pain and inflammation, its use may result in drug residues in dairy and other products of animal source aimed for human consumption. The present findings are also comparable with previous studies in which several other authors serious threats have been reported for long-term usage of low concentrations of DXM, having adverse effects on public health (Becker 2011; Reig *et al.* 2016). Additionally, its therapeutic use has also been limited due to the launching of MRLs in milk and edible tissues. DXM is 50 times more powerful than the steroid cortisol (Becker 2011). It has been stated that Fairclough *et al.* (1981) I.M administration of DXM most probably due to the formation of phosphate and acetate esters which can lead to the sustained release of DXM into the systemic circulation. Coelho *et al.* (1995) also reported that with the administration of phosphate and acetate esters plasma levels of DEX is also elevated. So, accumulation in plasma or muscles as from I.M. injections, one can surely expect residues in milk. DXM are administered to animals either by injections (parenterally), orally in feed/water, topically on the skin or by intramammary and intrauterine infusions and may lead to residues of drugs in foods of animal origin such as milk, meat, and eggs (Turnipseed *et al.* 2011). Calves fed milk and/or colostrum's from cows receiving drugs are also included in the cause list of residues (Guest and Paige 1991).

The result of the current study are also consistent with those observed by Falahatpisheh *et al.* (2011), who reported residues of DXM in cow milk *via* ELISA. Somewhat similar observations were also noticed by (Caloni *et al.* 2000; Parmar *et al.* 2021) who found residues of DEX in lactating cows after administration of a therapeutic dose of DXM once daily, they further stated that recommended doses exceeded the maximum residue limit of DXM and suggested a withdrawal period of 3–3.5 days in order to avoid its residues.

Effects of DEX on goat milk composition

DXM administration at therapeutic dose *i.e.*, 0.5 mg/kg BW once daily for three days, caused a significant increase in Fat content at 48 h and non-significant at 144 and 168 h post drug administration (Fig. 3). The fat slowly increased and

obtained peak level at 48 h then gradually it returned to decrease at 168 h. It has been reported that due to the lack of negative effect of DEX on fat's fluid secretion increased the concentration of fat in the treated cows (Varner and Johnson 2003). DEX significantly increased protein level at 48 h in goats and non-significant at 168 h after drug administration (Fig. 3). The concentration of protein increased then decreased and remained directly proportional to the changes in the milk yield. The secretion of protein was reduced after 48 h. The decline of unwanted effect of DEX on protein on fluid secretion clarifies the increase in the concentration of protein in the treated animals (Varner and Johnson 2003). The present finding for milk protein content was found in contrast to those observed by Shamay *et al.* (2000). They reported decreased level of protein in milk after induction of DXM in cows. This contrast may be attributed to interspecies differences between cow and goat. Similar findings were also reported by Varner and Johnson (2003) also reported similar finding, he reported that there is decreased level of protein content in milk composition. These variant findings may be due to climatic or nutritional factors which ultimately have caused increased protein level in current study.

The dose of 0.5 mg/kg BW of DEX showed a non-significant decrease in lactose content post drug administration (Fig. 3). The present findings of lactose content are in agreement with previous findings of Silanikove *et al.* (2006). They reported decreased level of lactose content in milk following DXM administration in cows. The basic cause in this decreased level of lactose in milk might be due to the relation between the activation of hypothalamic pituitary adrenal axis and reduction in the output of osmotic components from the alveoli into the gland lumen through the production of active biological substance from β-casein by the plasmin in the milk. This decreased level of lactose also may involve another factor such as decrease secretion of milk from glandular cells which resulted in reversion of lactose level to pre-treatment values in a directly proportional manner (Silanikove *et al.* 2006).

The therapeutic dose of 0.5 mg/kg BW of DEX initially exhibited non-significant increase in SNF. Later, SNF significantly increased from 16 to 120 h and then gradually returned to control level at 144 and 168 h post treatment (Fig. 3). The present result is in accordance with previous findings in which it has been reported that DXM Residues affected milk composition in various species (Shamay *et al.* 2000; Thanasak *et al.* 2004; Macrina *et al.* 2014). The current result of milk SNF content showed agreement with previous studies where it was also found increased level of SNF content in milk following DXM administration in the cows (Walsh *et al.* 1981). The basic cause in this increased level of SNF in milk might be due to the genetic potential of individual animals, age, stage of lactation, infections of udder and the type of feeding.

Milk Yield

In the present study milk yield non-significantly decreased by therapeutic administration of DXM in lactating goats till 16 h. Afterward, a significant decrease was observed in milk yield up to 144 h then returned to pretreatment level at 168 h (Fig. 4). Similar observation in agreement was also reported by Shamay *et al.* (2000), who recorded decreased in milk yield with the administration of a therapeutic dose of DXM in lactating cows. It has been reported that administration of ACTH and DXM to lactating cows caused a proportional decrease in milk yield (Hartmann and Kronfeld 2003). Reportedly, this decrease in milk yield might be due to the disruption of the cellular integrity of mammary epithelial cells of tight junctions which have caused lower milk yield in goats (Stelwagen *et al.* 2015). Another possible factor in which milk yield decreased may be attributed due to increase in milk sodium and chlorine due to their leakage from blood and decrease in potassium concentration which is leaked from milk to blood due to the administration of DEX (Stelwagen *et al.* 2014). It has been reported that dexamethasone treatment lowered mammary uptake of glucose, resulted in decreasing milk yield (Shamay *et al.* 2000).

Conclusion

It has been concluded from present study that the dexamethasone residues were found in the milk of goat up to 32 h then gradually decreased up to 168 h. Milk fat and protein increased at in 48 h then decreased till 168 h. Milk lactose showed non-significant increase which completely returned to pre-medication level at 48 h. Whereas, SNF of milk was increased upto 120 h and decreased at 168 h. Pulse rate, respiratory rate and rectal temperature increased during initial days later on, returned to control level at 168 h post DEX administration in goat.

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Author Contributions

MTK carried out the experiments; SB and RB planned the experiments, SS and GM analyzed the data, ZL conceived the experiment; MBA wrote the manuscript.

Conflicts of Interest

All authors declare no conflicts of interest.

Data Availability

The data will be made available on acceptable requests to the corresponding author.

Ethics Approval

Not applicable.

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