Thyroid hormones profile in Holstein calves following dexamethasone and isoflupredone administration

Chalmeh, A.*, Pourjafar, M., Nazifi, S., Zarei, M.R.

Department of Clinical Sciences, School of Veterinary Medicine, Shiraz University, Shiraz, Iran

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Correspondence
Chalmeh, A.
Department of Clinical Sciences, School of Veterinary Medicine, Shiraz University, Shiraz, Iran
Tel: +98(71) 36138700
Fax: +98(71) 32286940
Email: achalmeh81@gmail.com

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Abstract:

BACKGROUND: Glucocorticoids are the steroidal drugs which are very widely used in large animal medicine. These agents have advantages in large animals but they have also been associated with many potential adverse effects, especially at high doses or prolonged use. **OBJECTIVES:** The present experimental study was designed to clarify the effects of dexamethasone (DEXA) and isoflupredone (ISO), as the most common glucocorticoids in large animal medicine, on bovine thyroid hormones. **METHODS:** Ten clinically healthy Holstein calves (6-8 months old) were assigned into 2 equal groups. Dexamethasone (1 mg/kg) and isoflupredone (1 mg/kg) were administered intramuscularly in DEXA and ISOgroups, respectively, for two consecutive days. Blood samples were taken at days 0 (before the 1stdose), 1 (before the 2 nd dose), 2, 3, 5 and 7, from all studied animals and serum concentrations of T3, T4, fT3 and fT4 were determined in all specimens. **RESULTS:** Levels of T3 and T4 were decreased significantly after administration of both drugs. The concentrations of T3 and T4 in Iso group were significantly lower than the DEXA one ($p<0.05$). There were no significant changes in serum fT3 and fT4 levels following drug administration. **CONCLUSIONS:** Pharmacological doses of dexamethasone and isoflupredone have suppressive actions on the circulating levels of thyroid hormones in Holstein calves possibly via inhibition of TSH production at hypothalamic-pituitary-thyroid level.

Introduction

Several therapeutic agents can affect thyroid function at different levels (Betty, 2000; Bryan, 2009). These agents can alter circulating values of thyroid hormone by changing the levels of binding proteins or by competing for their hormone binding sites. Drugs may affect the synthesis or secretion of thyroid hormones. Pharmacological agents may also alter thyroid hormone metabolism and cellular uptake. Furthermore, drugs may interfere with hormone action at the target sites (Uma and Mihir, 2006). Hence, evaluating the circulating levels of thyroid hormones profile following the use of any medications can assist veterinarians to monitor the patients in order to prevent the side effects of drugs.

Glucocorticoids such as dexamethasone and isoflupredone are the steroidal drugs which are very widely used in large

animal medicine. These agents have anti-inflammatory and immunosuppressant properties which are critical for the treatment of a variety of diseases (Radostits et al., 2007). However, besides their benefits, glucocorticoids, especially at high doses or for prolonged period, have been associated with many potential adverse effects (Plumb, 2008). Researchers mentioned that if large doses of these agents are given for a long period of time it may reduce thyroid stimulating hormone secretion from anterior pituitary thereby decreasing thyroid hormone secretion by different mechanisms (Wilke and Utiger, 1969). Thyroid cell function can be regulated by glucocorticoids via changes in the concentrations of the pivotal bioregulators such as thyroid stimulating hormone (Kaminsky et al., 1994).

Literatures mentioned the effects of glucocorticoids on thyroid functions in human beings (Burr et al., 1976; Hosur et al., 2012), laboratory (Nyborg et al., 1984; Stachoń et al., 2014) and farm animals (Messer et al., 1995) but in spite of the common use of glucocorticoids in bovine medicine, information regarding the effects of these agents on thyroid hormones profile is rare in these animals. Hence, the present experimental study was performed to clarify the effects of dexamethasone and isoflupredone on circulating levels of triiodothyronine (T3), thyroxine (T4), free triiodothyronine (fT3) and free thyroxine (fT4) in clinically healthy Holstein calves.

Materials and Methods

In October 2013, 10 clinically healthy Holstein calves (6-8 months old) were selected from two different dairy farms around Shiraz, Iran. The animals were examined prior to study and were proved to be clinically healthy. Calves were assigned into 2 equal groups (n=5). Dexamethasone (Vetacoid® 0.2%, Aburaihan Pharmaceutical Co, Tehran, Iran, 1 mg/kg, intramuscularly) and isoflupredone (Vetapredone® 0.2%,Aburaihan Pharmaceutical Co, Tehran, Iran, 1 mg/kg, intramuscularly) were administered in DEXA and ISO groups, respectively, for two consecutive days. Blood samples were taken at days 0 (before the 1stdose), 1 (before the 2nddose), 2, 3, 5 and 7 from all calves through the jugular vein in plain tubes. Immediately after blood collections, sera were separated by centrifugation (10 minutes at 3,000×g) and stored at −22°C until assayed.

Serum T3 concentrations were determined using a competitive enzyme immunoassay kit (Padtan Elm Co., Tehran, Iran). The intra- and inter-assay CVs were 12.6% and 13.2%, respectively. The sensitivity of the test was 0.2 ng/mL. Serum T4 concentrations were measured using a competitive enzyme immunoassay kit (Monobind Inc., CA, USA). The intra- and inter-assay CVs were 3.0% and 3.7%, respectively. The sensitivity of the test was 0.4 mg/dl. Serum fT3 and fT4 concentrations were determined by the fT3 and the fT4 ELISA kits (DiaPlus Inc., San Francisco, CA, USA). The intra- and inter-assay CVs of the fT3 assays were 4.1% and 5.2%, respectively. The sensitivity of the test was 0.05 pg/ml. The intra- and inter-assay CVs of the fT4 assays were 4.5% and 3.7%, respectively. The sensitivity of this test was 0.05 ng/dl, too.

Data were expressed as mean ± standard error (SE). Statistical analysis was performed using two independent samples t-test to compare mean concentrations of thyroid hormones within similar hours between experimental groups. Repeated mea-

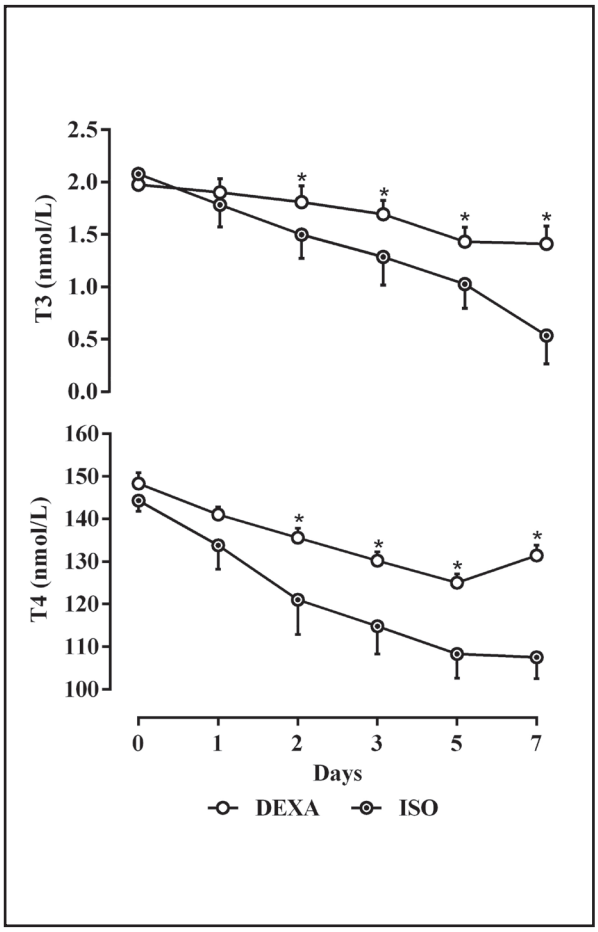

Figure 1. Effects of dexamethasone and isoflupredone (both at 1 mg/kg, injected intramuscularly for two consecutive days) on serum T3 and T4 levels in clinically healthy Holstein calves. Stars indicate significant differences between groups on similar days ($p<0.05$).

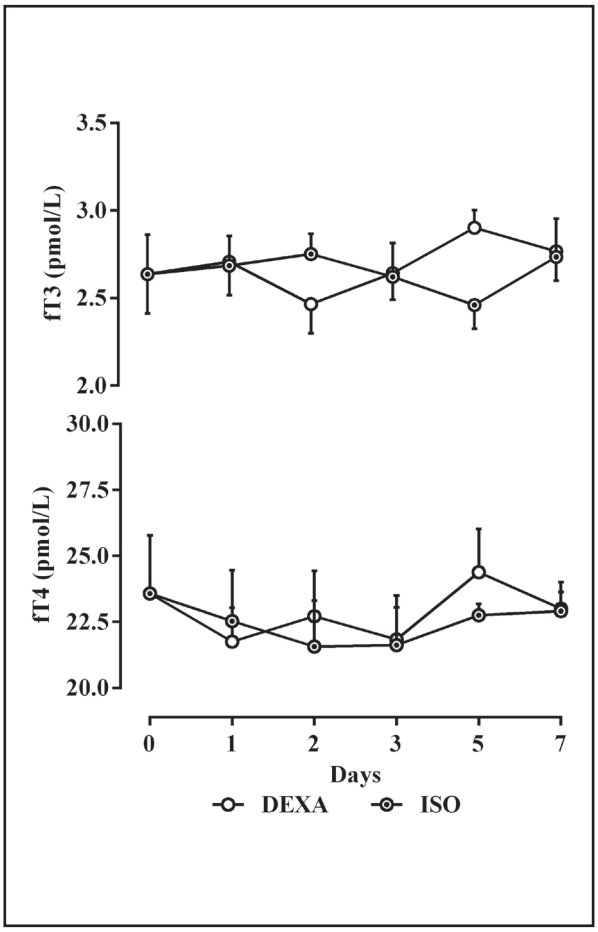

Figure 2. Effects of dexamethasone and isoflupredone (both at 1 mg/kg, injected intramuscularly for two consecutive days) on serum fT3 and fT4 levels in clinically healthy Holstein calves. Stars indicate significant differences between groups on similar days ($p<0.05$).

sures ANOVA was also used in order to study the changes in pattern of serum thyroid hormones in each group, using SPSS software (SPSS for Windows, version 11.5, SPSS Inc, Chicago, Illinois). The level of significance was set at $p<0.05$.

Results

Effects of dexamethasone and isoflupredone on serum thyroid hormones of clinically healthy Holstein calves are presented in Figs. 1 and 2. Levels of T3 and T4 were decreased significantly after both drugs were administrated ($p<0.05$). The decreasing pattern of T3 and T4 were continued to last blood sampling at day 7 and their concentrations did not reach base line values at day zero. The concentrations of T3 and T4 in ISO group were significantly lower than those of DEXA group ($p<0.05$; Figure 1). There were no significant changes in patterns in serum fT3 and fT4 levels following drug administration. Furthermore, no significant differences were seen between groups at all similar hours ($p>0.05$; Figure 2).

Discussion

Thyroid gland produces the thyroid hormones containing T3 and its prohormone, T4, which are tyrosine-based hormones.

Thyrotropes of the anterior pituitary gland secrete thyroid stimulating hormone (TSH) and this hormone regulates the production of T3 and T4 by follicular cells of the thyroid gland. T4 is the major circulating thyroid hormone which has a longer half-life than T3. T4 is changed to T3 which is more potent than T4. fT3 and fT4 represent the amount of T3 and T4 that are not bound to proteins. Evaluating the fT3 and fT4 can be used to assess and manage disorders of the thyroid gland (Yen, 2001).

Thyroid hormones are primarily responsible for metabolism regulation. They increase the metabolic rate, change protein synthesis, regulate osteoblasts and nervous system maturation and increase the sensitivity to catecholamines. The proper circulating levels of thyroid hormones are necessary to develop and differentiate all of the cells. These hormones are also responsible for regulation of protein, fat, carbohydrate and vitamin metabolism. Numerous physiological, pathological and pharmacological stimuli influence thyroid hormone metabolism (Taylor et al., 1997; Tan et al., 1998).

We hypothesized that glucocorticoids, as a common pharmacological agent in large animals, can potentially affect the thyroid hormones profile. Hence the present experimental study was performed to compare the effects of dexamethasone and isoflupredone on the metabolism of thyroid hormones in clinically healthy Holstein calves. The results of the current research showed that circulating levels of T3 and T4 in both DEXA and ISO groups were decreased significantly after glucocorticoids administration.

All of the researchers mentioned that administration of glucocorticoids suppress the thyroid hormones. Glucocorticoids decreased blood serum TSH concentrations in euthyroid women (Bános et al., 1979). Dexamethasone administration to hypothyroid rats decreased serum TSH. Dexamethasone augmented a T3-induced decrease of TSH. However, changes in pituitary TSH α- and β-subunit mRNA concentrations were not found (Ahlquist et al., 1989).

Kakucska et al. (1995) obtained clearer results on the effects of glucocorticoids on the hypothalamo-pituitary-thyroid axis. In the paraventricular hypothalamic nuclei of adrenalectomized rats, an increase in corticotropin releasing hormone mRNA occurred in parallel to the increase in pro-thyrotropin releasing hormone mRNA. On the contrary, administration of corticosterone or dexamethasone caused a marked decrease in corticotropin releasing hormone mRNA and pro-thyrotropin releasing hormone mRNA (Kakucska et al., 1995).

Administration of a single dose of hydrocortisone (500 mg) increased both TSH production and stimulation by thyrotropin releasing hormone in normal subjects and patients with Cushing's syndrome (Rubello et al., 1992). Only long-term hypocorticism may be a cause for decreased TSH level. The earlier recovery of the diurnal rhythm of TSH than that of cortisol suggests that the TSH rhythm is not under the direct control of circulating cortisol (Azukizawa et al., 1979). Fang and Shian (1981) suggested that adrenal glands may not be directly involved in the hypothalamic control of the pituitary content of TSH. They also revealed that physiological levels of glucocorticoids clearly exert an inhibitory effect on TSH release by the pituitary gland in response to provocative stimulation.

Administration of a high dose of dexamethasone not only suppressed TSH but also decreased the TSH response to thyrotropin

releasing hormone administration (Re et al., 1976).The inhibitory effect of dexamethasone is used for monitoring of subclinical hypothyroidism in obese patients. Administration of thyrotropin releasing hormone after dexamethasone increased the TSH level only in hypothyroid patients but not in euthyroid obese patients (Coiro et al., 2001). Results of the Ghadhban and Jawad's study (2013) revealed a significant decrease in the serum concentrations of T3 and T4 during administration of dexamethasone in rabbits at 0.5 mg/kg BW. This decrease in the thyroid hormones of rabbit circulation may be due to dexamethasone action as suppression of hypothalamic-pituitary-thyroid activity.

In conclusion, it can be stated that pharmacological doses of dexamethasone and isoflupredone have suppressive actions on the circulating levels of active thyroid hormone in Holstein calves. Based on the findings of other researchers it may be suggested that the common pathway of this action is at hypothalamic-pituitary-thyroid level to inhibit TSH production and hence reduce thyroidal T3 and T4 release. The results of the present experimental study showed that decreasing the serum T3 and T4 levels can be considered as a side effect of glucocorticoids in Holstein calves and veterinarians should note the disadvantages of these pharmacological agents.

Acknowledgments

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References

Ahlquist, J., Franklyn, J., Ramsden, D., Sheppard, M. (1989) The influence of dexamethasone on serum thyrotrophin and thyrotrophin synthesis in the rat. Mol Cell Endocrinol. 64: 55-61.

Azukizawa, M., Mori, S., Ohta, H., Matsumura, S., Yoshimoto, H., Uozumi, T., Miyai, K., Kumahara, Y. (1979) Effect of a single dose of glucocorticoid on the diurnal variations of TSH, thyroxine, 3,5,3'-triiodothyronine, 3,3',5'-triiodothyronine and cortisol in normal men. Endocrinol Jpn. 26: 719-723.

Bános, C., Takó, J., Salamon, F., Györgyi, S., Czikkely, R. (1979) Effect of ACTH-stimulated glucocorticoid hypersecretion on the serum concentrations of thyroxine-binding globulin, thyroxine, triiodothyronine, reverse triiodothyronine and on the TSH response to TRH. Acta Med Acad Sci Hung. 36: 381-394.

Betty, J.D. (2000) How medications affect thyroid function. West J Med. 172: 102-106.

Bryan, R.H. (2009) Drugs that suppress TSH or cause central hypothyroidism. Best Pract Res Clin Endocrinol Metab. 23: 793-800.

Burr, W.A., Ramsden, D.B., Griffiths, R.S., Hottenberg, R., Meinhold, H., Wenzel, K.W. (1976) Effects of a single dose of dexamethasone on serum concentration of thyroid hormone. Lancet. 308: 58-61.

Coiro, V., Volpi, R., Capretti, L., Speroni, G., Pilla, S., Cataldo, S., Bianconcini, M., Bazzani, E., Chiodera, P. (2001) Effect of dexamethasone on TSH-secretion induced by TRH in human obesity. Investig Med. 49: 330-334.

Fang, V., Shian, L. (1981) Adrenal influence on pituitary secretion of thyrotropin and prolactin in rats. Endocrinology. 108: 1545-1551.

Ghadhban, R.F., Jawad, A.D.H. (2013) Effects of dexamethasone, estrogen administration on leptin, thyroid, reproductive hormone concentration and lipid profile of female rabbit's serum. Bas J Vet Res. 12: 41-53.

Hosur, M.B., Puranik, R.S., Vanaki, S., Puranik, S.R. (2012) Study of thyroid hormones free

triiodothyronine (FT3), free thyroxine (FT4) and thyroid stimulating hormone (TSH) in subjects with dental fluorosis. Eur J Dent. 6: 184-190.

Kakucska, I., Qi, Y., Lechan, R. (1995) Changes in adrenal status affect hypothalamic thyrotropin-releasing hormone gene expression in parallel with corticotropin-releasing hormone. Endocrinology. 136: 2795-2802.

Kaminsky, S., Levy, O., Salvador, C., Dai, G., Carrasco, N. (1994) Na(+)-I- symport activity is present in membrane vesicles from thyrotropin-deprived non-I(-)-transporting cultured thyroid cells. Proc Natl Acad Sci. 91: 3789-3793.

Messer, N.T., Ganjam, V.K., Nachreiner, R.F., Krause, G.F. (1995) Effect of dexamethasone administration on serum thyroid hormone concentrations in clinically normal horses.J Am Vet Med Assoc. 206: 63-66.

Nyborg, J.K., Nguyen, A.P., Spindler, S.R. (1984) Relationship between thyroid and glucocorticoid hormone receptor occupancy, growth hormone gene transcription, and mRNA accumulation. J Biol Chem. 259: 12377-12381.

Plumb, D.C. (2008) Plumb's Veterinary Drug Handbook. (6th ed.) Blackwell Publishing. Iowa, USA. p. 457-639.

Radostits, O.M., Gay, C., Hinchcliff, K.W., Constable, P.D. (2007) Veterinary Medicine: A Textbook of the Diseases of Cattle, Horses, Sheep, Pigs and Goats. (10th ed.) Saunders. London, UK. p. 53-60.

Re, R., Kourides, I., Ridgway, E., Weintraub, B., Maloof, F. (1976) The effect of glucocorticoid administration on human pituitary secretion of thyrotropin and prolactin. J Clin Endocrinol Metab. 43: 338-346.

Rubello, D., Sonino, N., Casara, D., Girelli, M., Busnardo, B., Boscaro, M. (1992) Acute and chronic effects of high glucocorticoid levels on hypothalamic-pituitary-thyroid axis in man. J Endocrinol Invest. 15: 437-441.

Stachoń, M., Gromadzka-Ostrowska, J., Lachowicz, K., Fürstenberg, E., Pałkowska, E., Gajewska, D., Myszkowska-Ryciak, J., Kozłowska, L., Rosołowska-Huszcz, D. (2014) Interdependence of the peripheral metabolism of glucocorticoids and thyroid hormones under calorie deficit in rats at different ages. J Anim Feed Sci. 23: 167-176.

Tan, K.C., Shiu, S.W., Kung, A.W. (1998) Effect of thyroid dysfunction on high-density lipoprotein subfraction metabolism: roles of hepatic lipase and cholesteryl ester transfer protein. J Clin Endocrinol Metab. 83: 2921-2924.

Taylor, A.H., Stephan, Z.F., Steele, R.E., Wong, N.C. (1997) Beneficial effects of a novel thyromimetic on lipoprotein metabolism. Mol Pharmacol. 52: 542-547.

Uma, K.S., Mihir, S. (2006) Drug induced thyroid disorders. J Indian Med Assoc: 104, 583, 585-587, 600.

Wilke, J.F., Utiger, R.D. (1969) The effect of glucocorticoids on thyrotropin secretion. J Clin Invest. 48: 2086-2090.

Yen, P.M. (2001) Physiological and molecular basis of thyroid hormone action. Physiol Rev. 81: 1097-1142.

مجله طب دامی ایران، ۱۳۹۶، دوره ۱۱، شماره ۱، ۵۴-۴۹

پروفایل هورمون‌های تیروئیدی متعاقب تجویز ایزوفلوپردون و دگزامتازون در گوساله‌های هلشتاین

علی اصغر چالمه* مهرداد پورجعفر سعید نظیفی محمد رضا زارعی

گروه علوم درمانگاهی، دانشکده دامپزشکی دانشگاه شیراز، شیراز، ایران

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چکیده

زمینه مطالعه: گلوکوکورتیکوئیدها داروهای استروئیدی هستند که به طور گسترده در طب دام‌های بزرگ مورد استفاده قرار می‌گیرند. این داروها منافع متعددی در دام‌های بزرگ دارند اما مضراتی نیز در استفاده طولانی مدت یا در مقادیر بالا ممکن است مشاهده شود. **هدف:** مطالعه تجربی حاضر به منظور مشخص ساختن تأثیر دگزامتازون و ایزوفلوپردون، به عنوان دو گلوکوکورتیکوئید رایج در دام‌های بزرگ، بر هورمون‌های تیروئیدی گاو انجام شد. **روش کار:** تعداد ۱۰ رأس گوساله هلشتاین به ظاهر سالم (۶ تا ۸ ماهه) در دو گروه مساوی وارد شدند. دگزامتازون (۱mg/kg) و ایزوفلوپردون (۱mg/kg) به ترتیب به گروه‌های دگزا و ایزو در دو روز متوالی از طریق داخل عضلانی تجویز شدند. نمونه‌های خون در روز صفر (قبل از اولین تجویز دارو)، ۱ (قبل از دومین تجویز دارو)، ۲، ۳، ۵ و ۷ از تمام حیوانات مورد مطالعه اخذ شد و غلظت های سرمی T۳، T۴، fT۳ و fT۴ در تمامی نمونه‌ها مورد سنجش قرار گرفت. **نتایج:** مقادیر T۳ و T۴ به طور معنی‌داری پس از تجویز هر دو دارو کاهش یافت. میزان T۳ و T۴ در گروه ایزو به طور معنی‌داری کمتر از دگزا بود ($p<۰/۰۵$). تغییرات معنی‌داری در سطوح سرمی fT۳ و fT۴ متعاقب تجویز این داروها مشاهده نشد. **نتیجه‌گیری نهایی:** مقادیر فارماکولوژیک دگزامتازون و ایزوفلوپردون اثرات مهاری بر سطوح سرمی هورمون‌های تیروئیدی گوساله‌های هلشتاین داشت که احتمالاً از طریق مهار تولید TSH در سطح هیپوتالاموس-هیپوفیز-تیروئید است.

واژه های کلیدی: گلوکوکورتیکوئیدها، گوساله های هلشتاین، متابولیسم، عوارض جانبی ، هورمون‌های تیروئیدی

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*) نویسنده مسؤول: تلفن: ۳۶۱۳۸۷۰۰ (۷۱)۹۸+ نمابر: ۳۲۲۸۶۹۴۰ (۷۱)۹۸+ Email: achalmeh81@gmail.com